Basics of Resting State fMRI

Intrinsic Activity
Endogenous Oscillations
Spontaneous Fluctuations
Task Independent Fluctuations
Low Frequency Fluctuations
Default Mode

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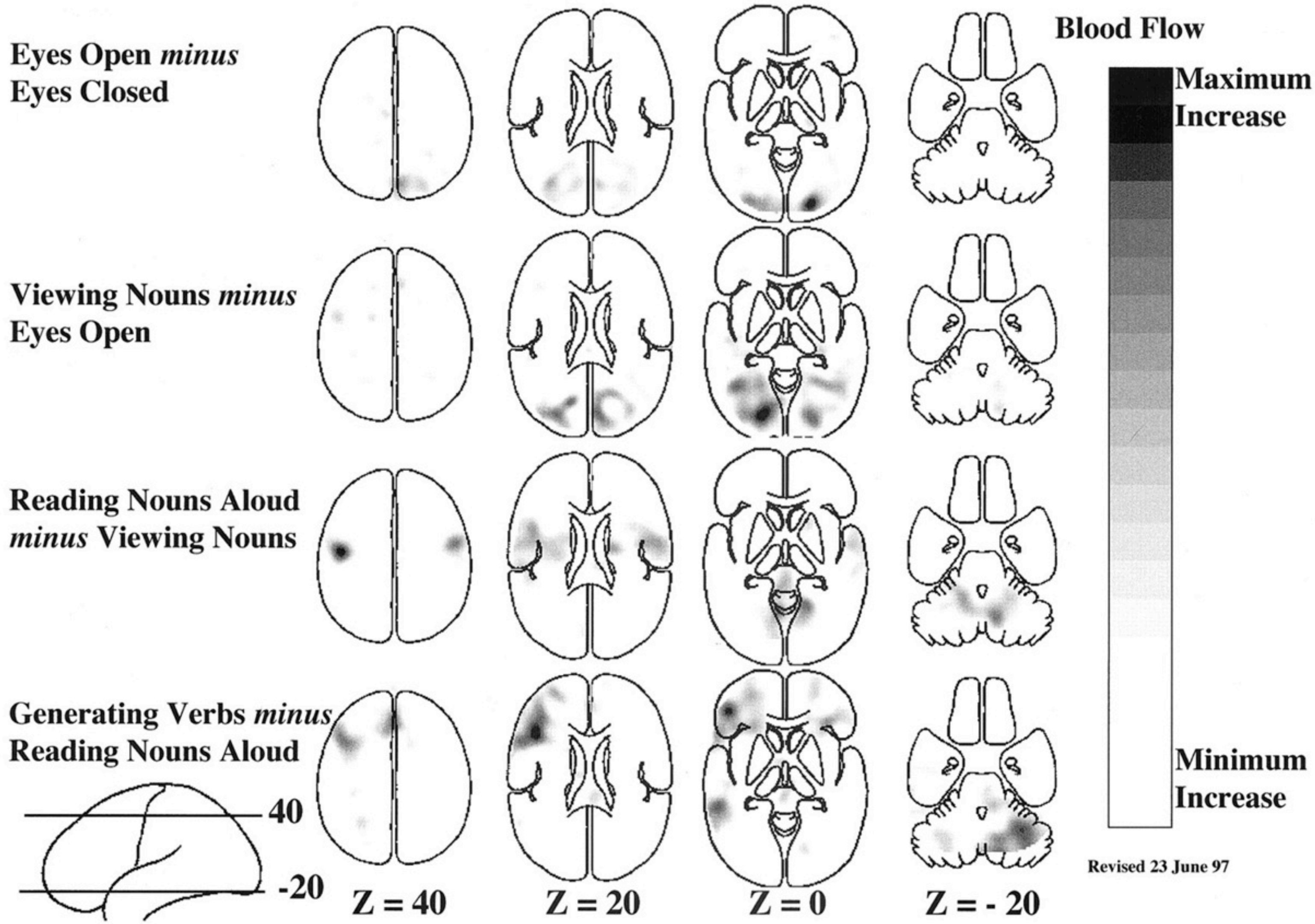
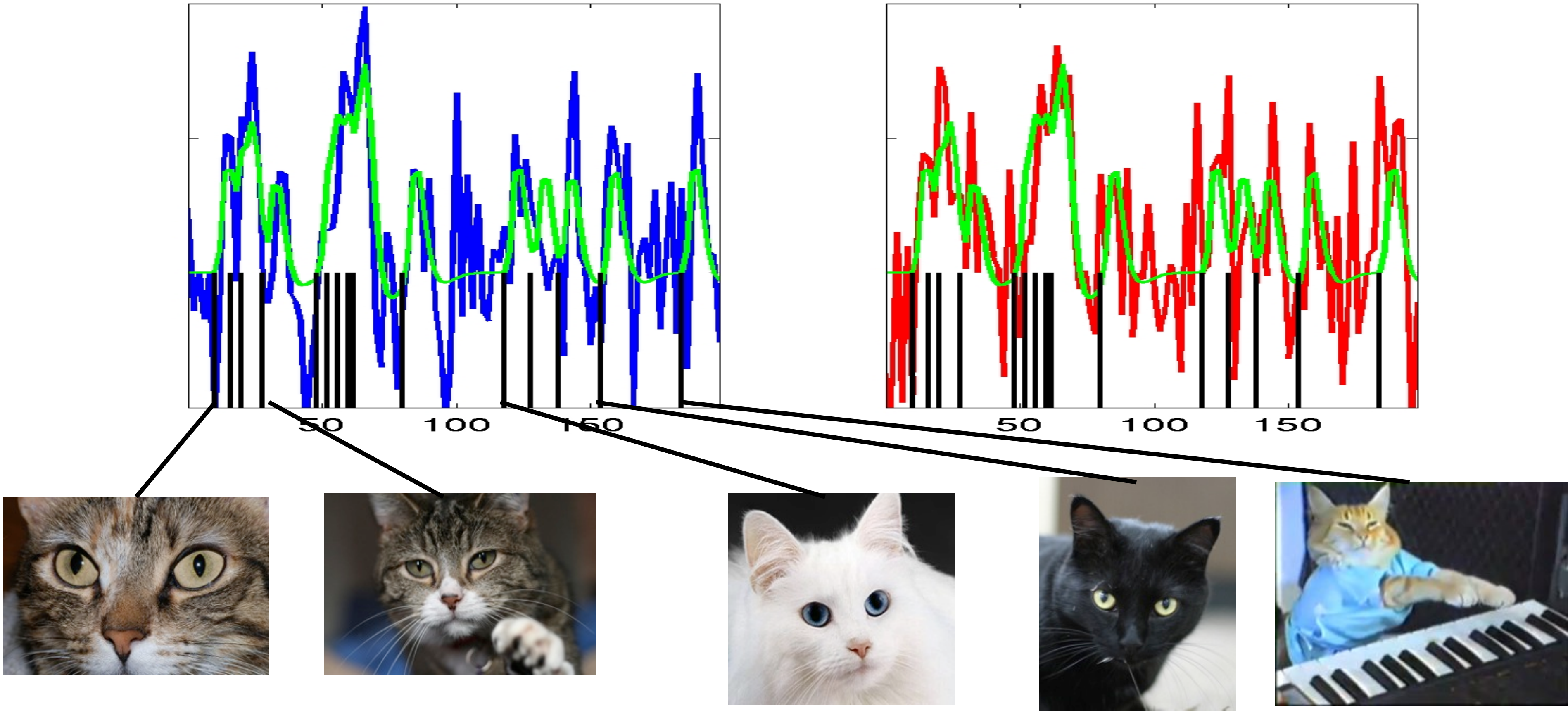
July 12, 2013

Task-based neuroscience



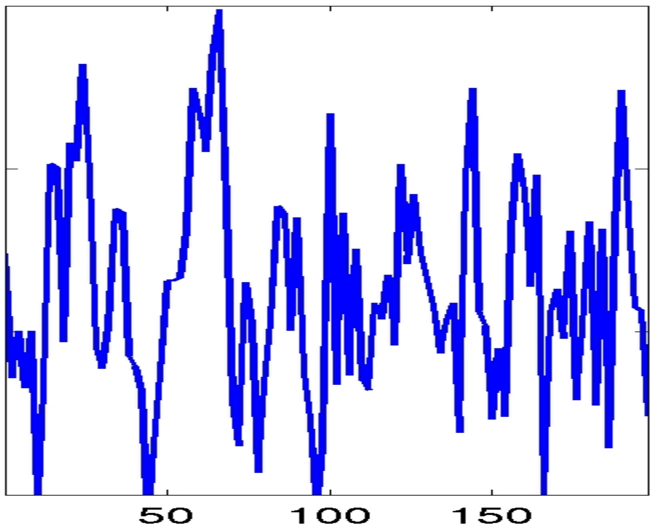
Using PET Data from the mid 1980's
Raichle PNAS 1998;95:765-772

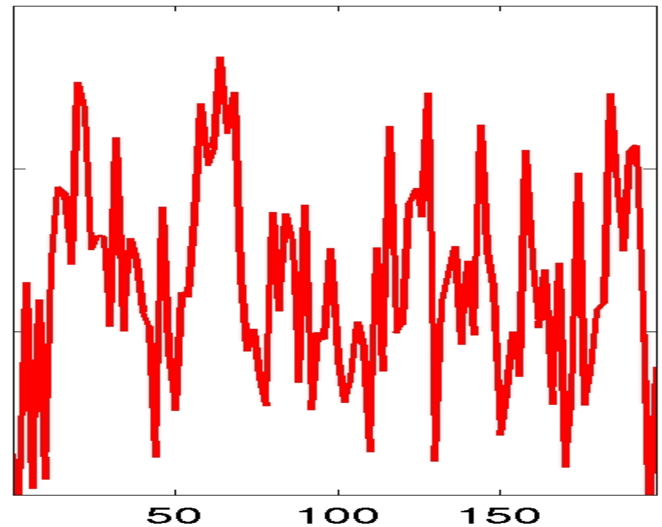
Task-based fMRI



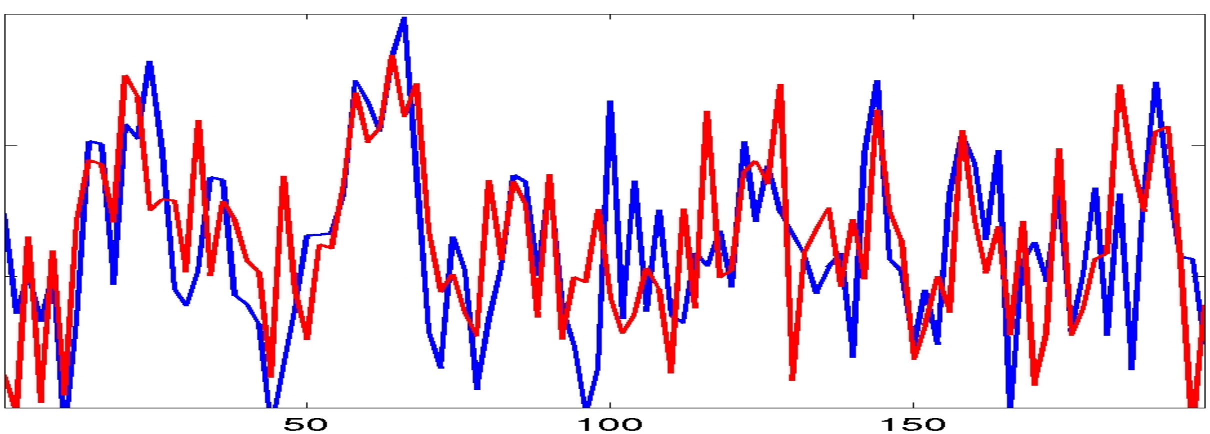
Cat images from Wikipedia

Resting State fMRI



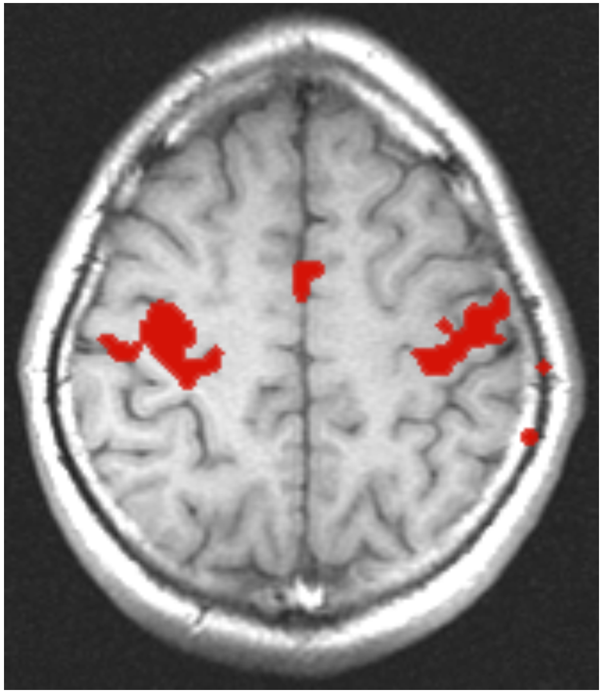


"Resting State fMRI is just task-based fMRI when you don't know the task" –Larry Wald

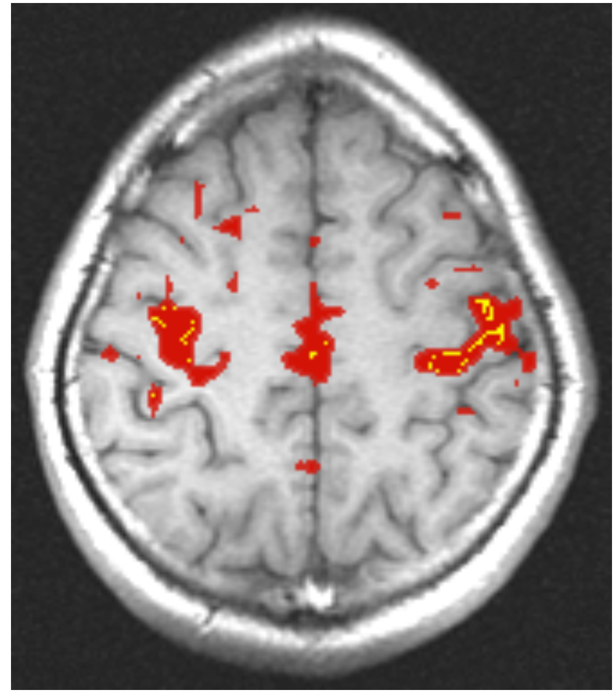


r=0.56

We don't need a task to get blobs



Activation during finger-tapping

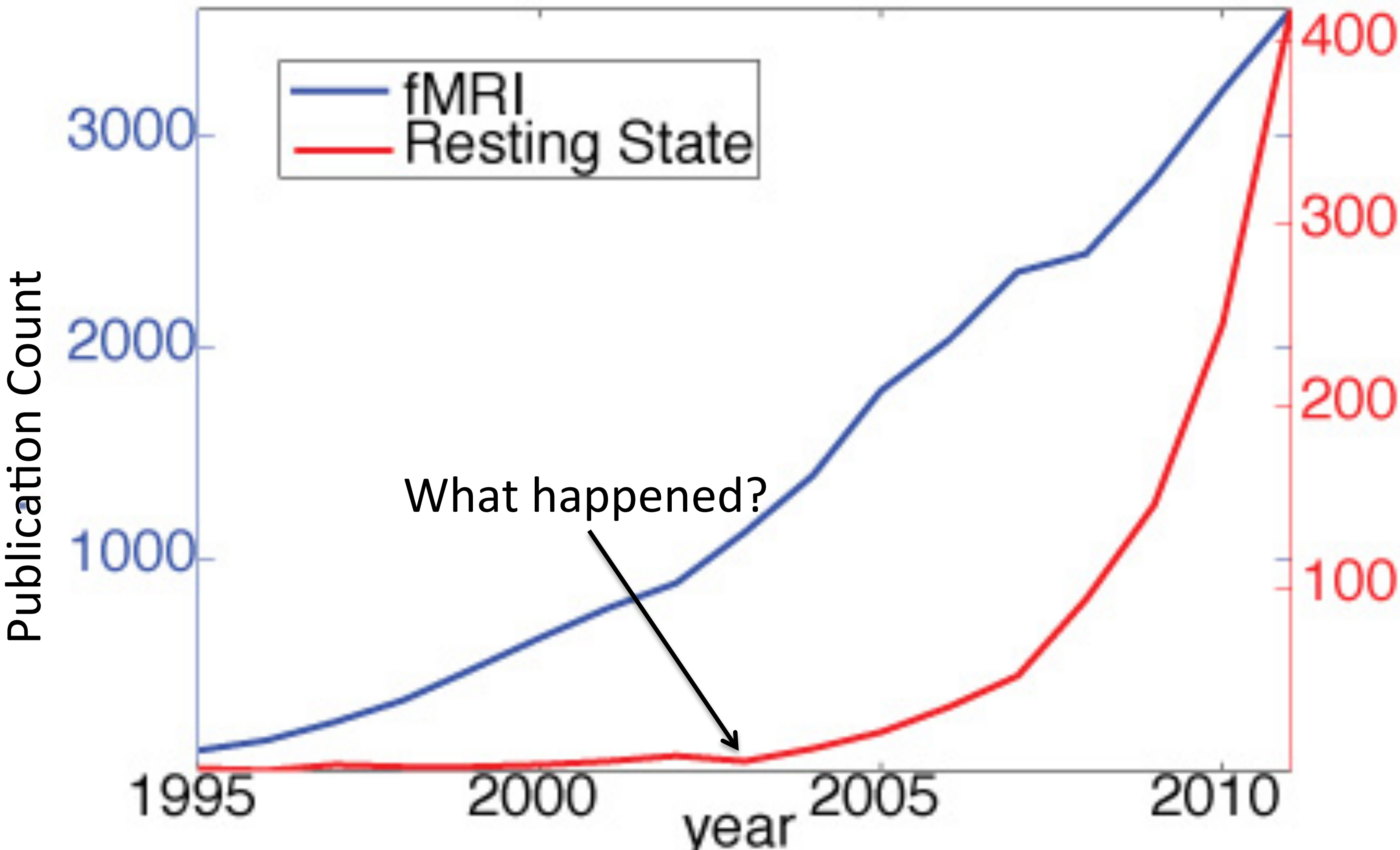


Correlations with "seed voxel" in motor cortex **during rest**

B. Biswal *et al., MRM, 34:537 (1995)*

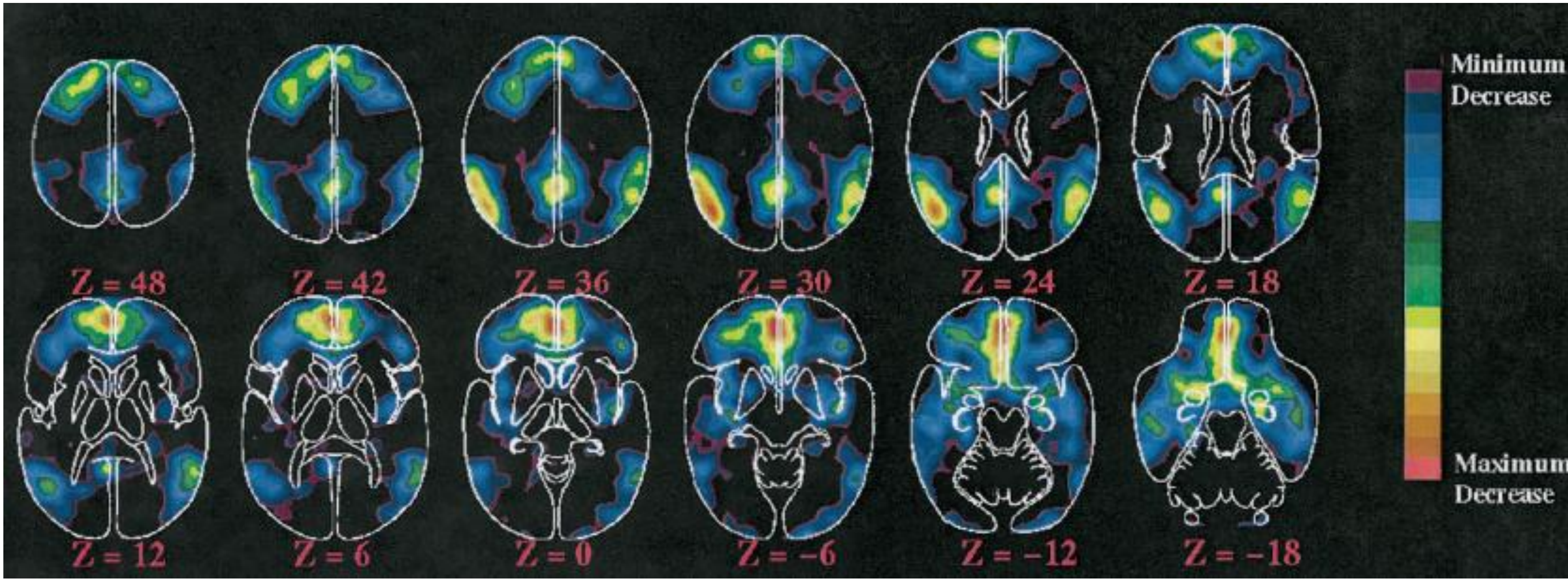
Task-based significance shows how brain regions respond
Connectivity shows how brain regions interact.

fMRI and resting state publications



fMRI from PubMed. Resting state from a curated list by a Child Mind Institute Librarian
Data provided by Matthew Doherty of CMI

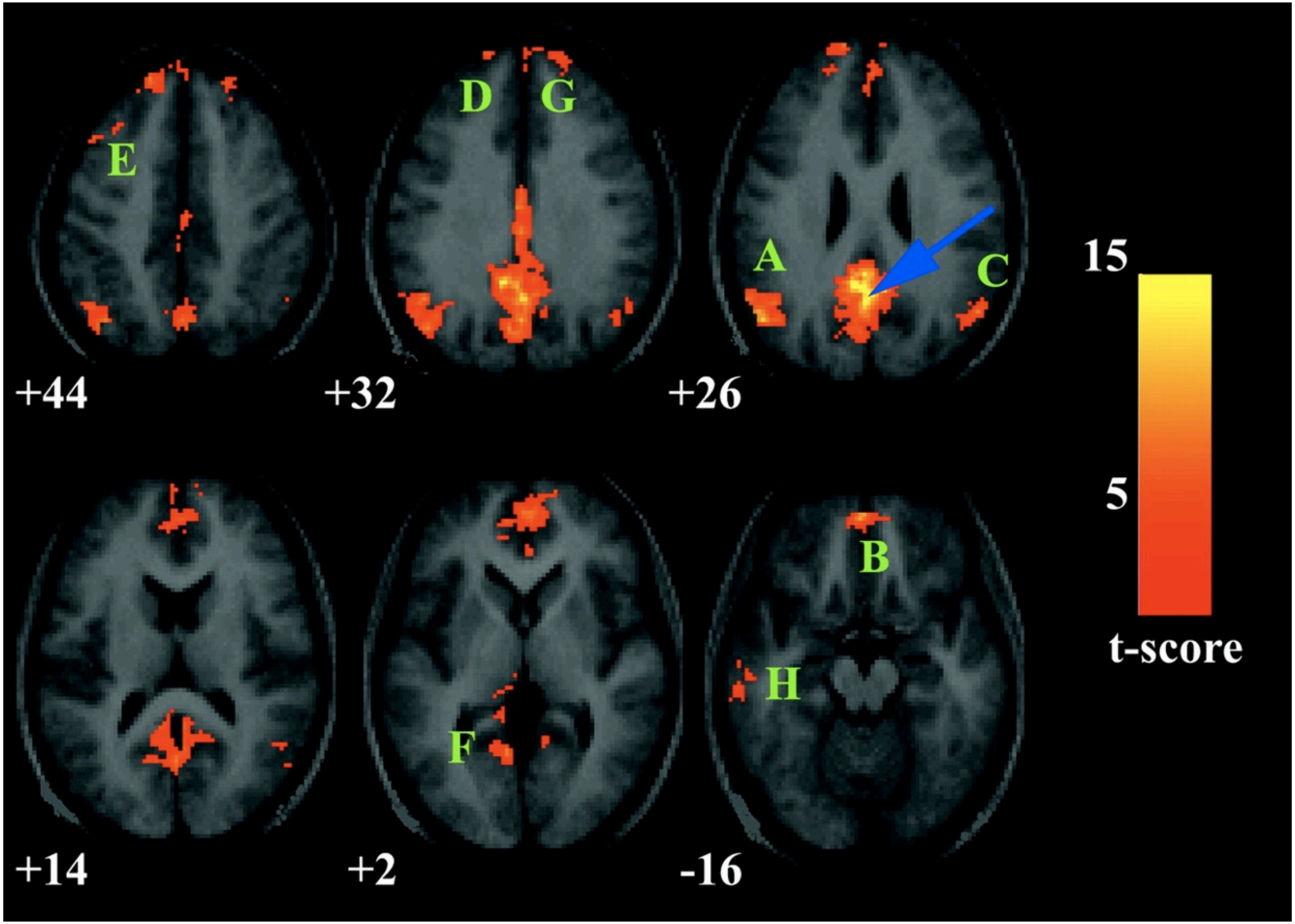
The Default Mode Network



For many tasks, a common group of brain areas shows more activation in the "rest" compared to the task condition.

Raichle et al PNAS 2001

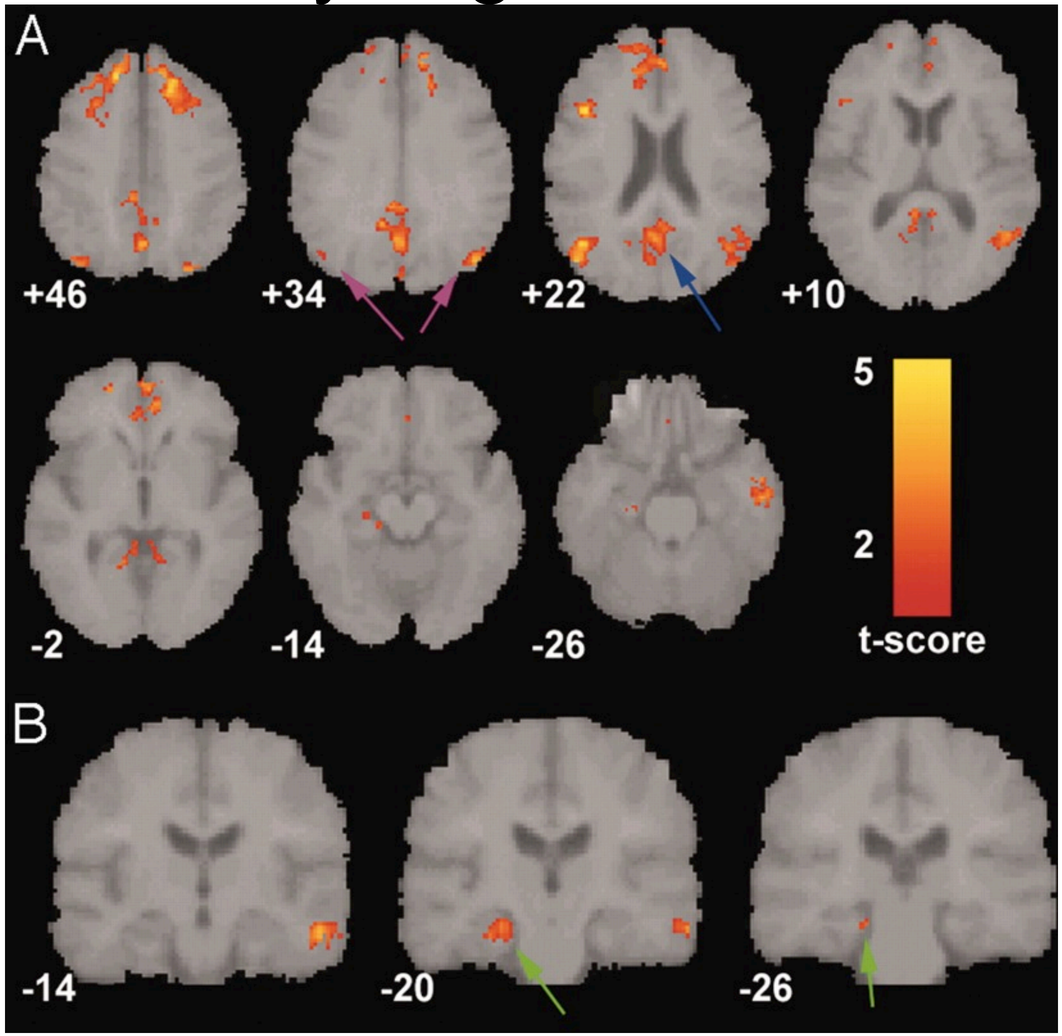
The Default Mode Network



Default mode regions show significant temporal correlations using fMRI

Greicius M D et al. PNAS 2003;100:253-258

Resting connectivity might have clinical relevance

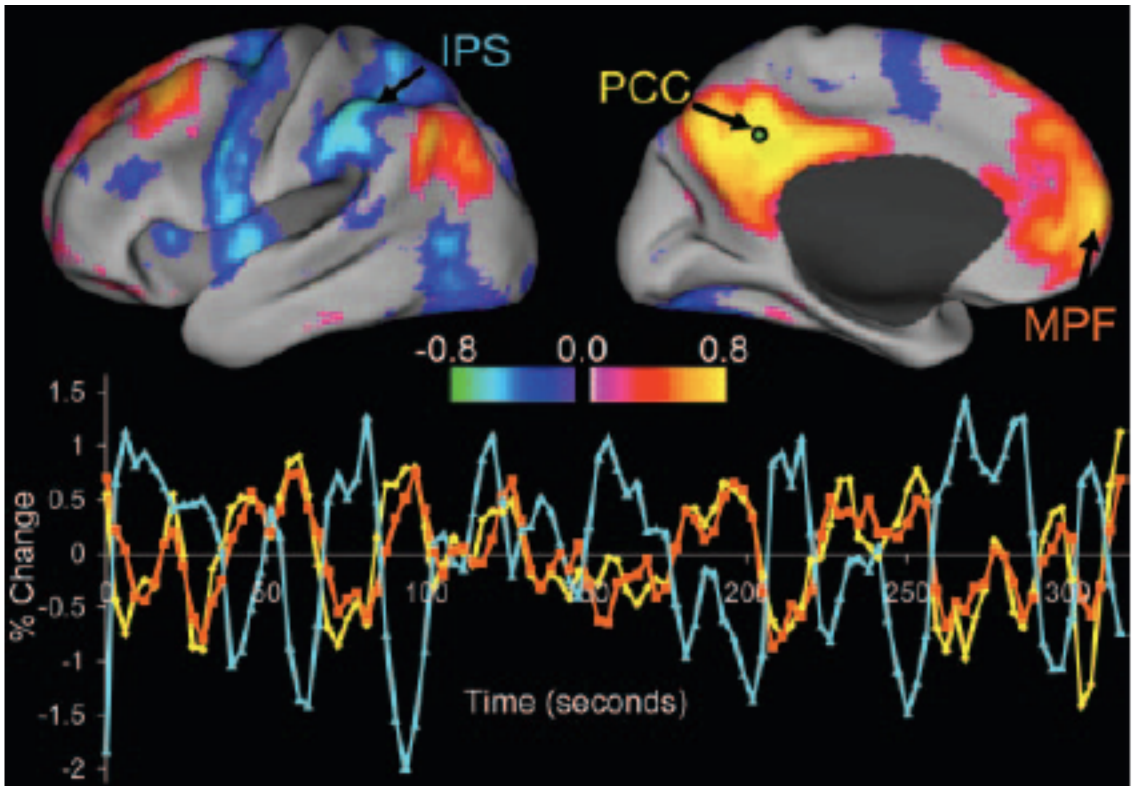


Default mode brain regions distinguish Alzheimer's Disease patients from healthy elderly

Greicius M D et al. PNAS 2004;101:4637-4642

Big new visions of the brain organization

The human brain is intrinsically organized into dynamic, anticorrelated functional networks



Fox et al, *PNAS 102, 2005*

This is exciting!!!

No need for tasks!

No need to worry if your volunteer performs the task!

Just throw someone in the scanner and tell them to sit still for 5 minutes!

Get any brain networks you want to study!

People will get Neuro or Psych PhDs without ever running task-based experiments!

(This has probably already happened)

fMRI for Epidemiology is Practical

- **ADHD-200**: 491 typically developing (TD) and 285 ADHD children's resting scans from 8 sites
  http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html
- **ABIDE**: 573 TD and 539 Autism Spectrum Disorder children's resting scans from 16 sites
  http://fcon_1000.projects.nitrc.org/indi/abide/
- **Nathan Kline Institute Enhanced Rockland Sample**
  Randomly selected large age-spectrum sample (1000+ people) from a NY county is being collected & rapidly shared
  http://fcon_1000.projects.nitrc.org/indi/enhanced/

Is it really THAT exciting?

What are the challenges?

Really. What are they?

Did you think this was going to be another list of bullet points answering this question?

Some challenges

What exactly do we collect?

Trying to isolate the neural signal
(Attend Catie Chang's and Steve Gotts' talks)

How do we know the remaining signal is neural?

Method Selection & Applications when everything looks good and there are few definitively correct results

What do we collect?

What is “resting state”?

Awake/Asleep?

Eyes open/closed?

Lighting in room?

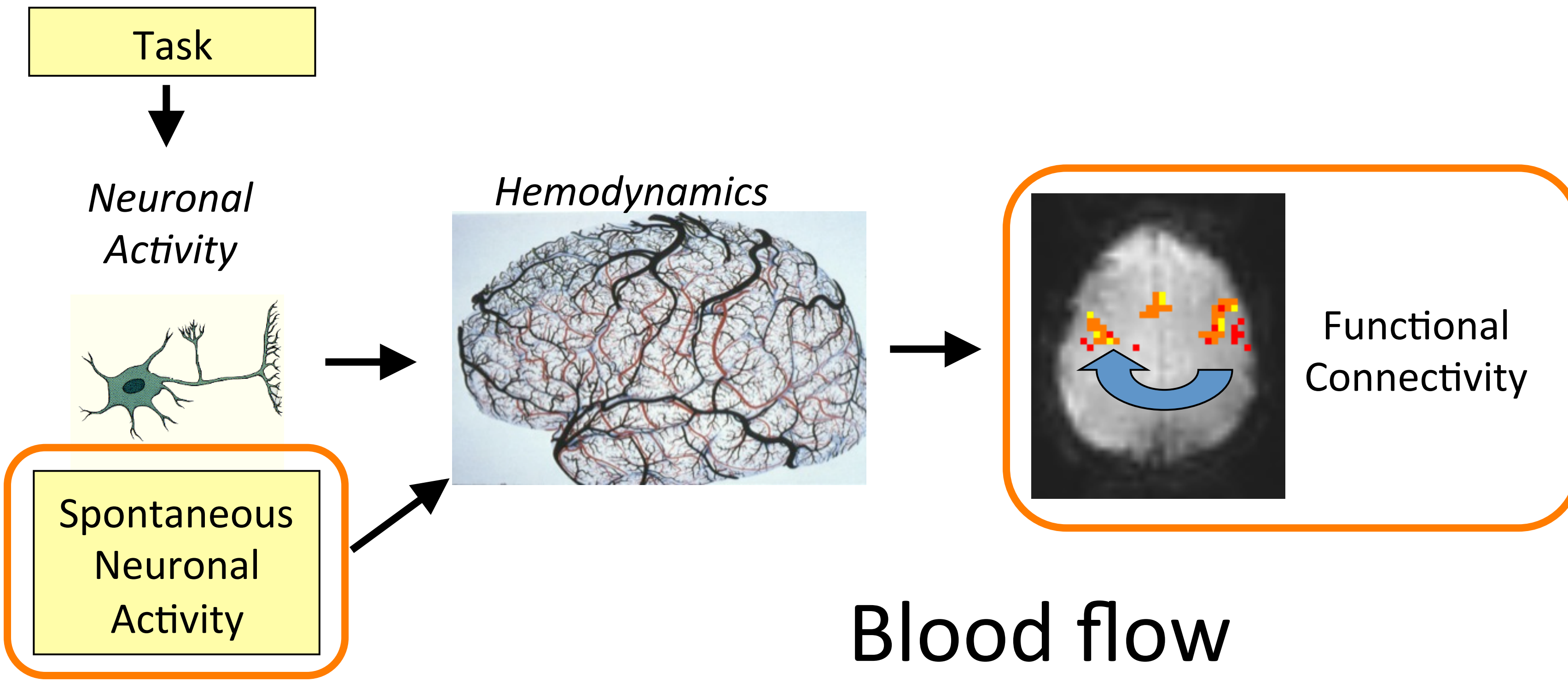
Low level tasks?

What do you tell the volunteer not to do?

What do we collect?

- How long to scan?
  - What gives us stable results?
  - Are the instabilities interesting (connectivity dynamics)?
- How much do scanning parameters matter?
  - Voxel size, in-slice acceleration, flip angle, TR, TE, …
- When to scan?
  - Time of day
  - Preceding activities
- What can alter results?
  - How can we increase confidence that population differences are neural?

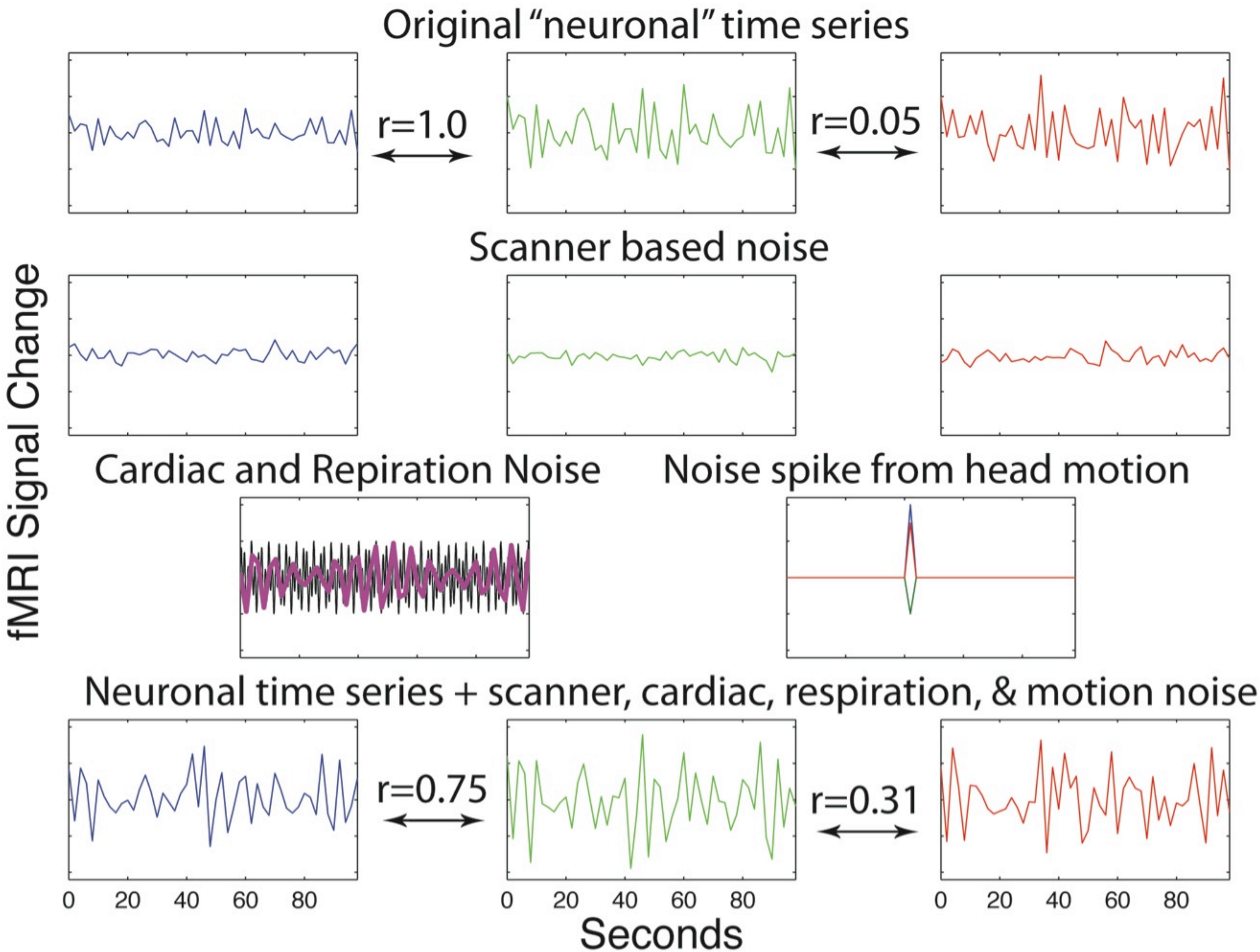
Isolating the neural signal



Blood flow
Movement
Scanner Artifacts

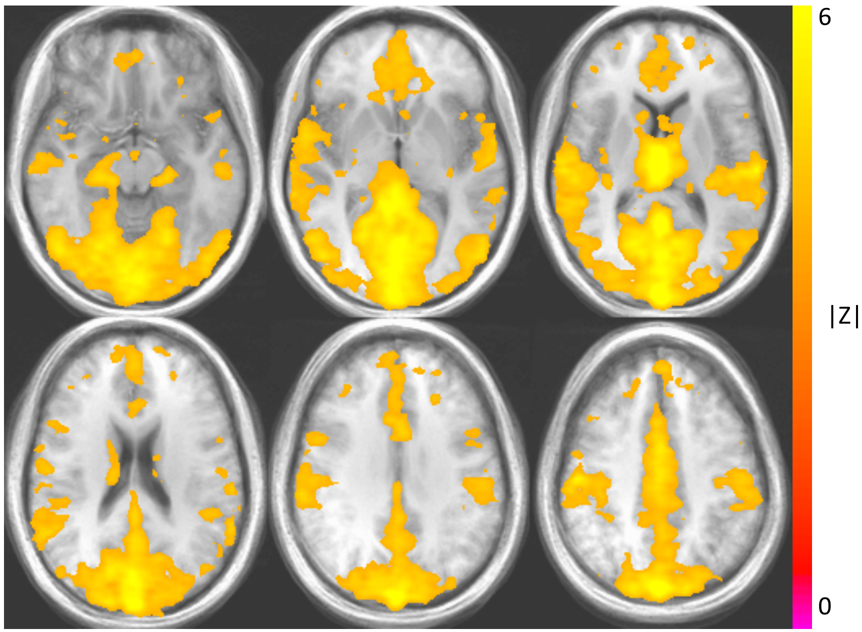
Slide from Rasmus Birn

Isolating the neural signal

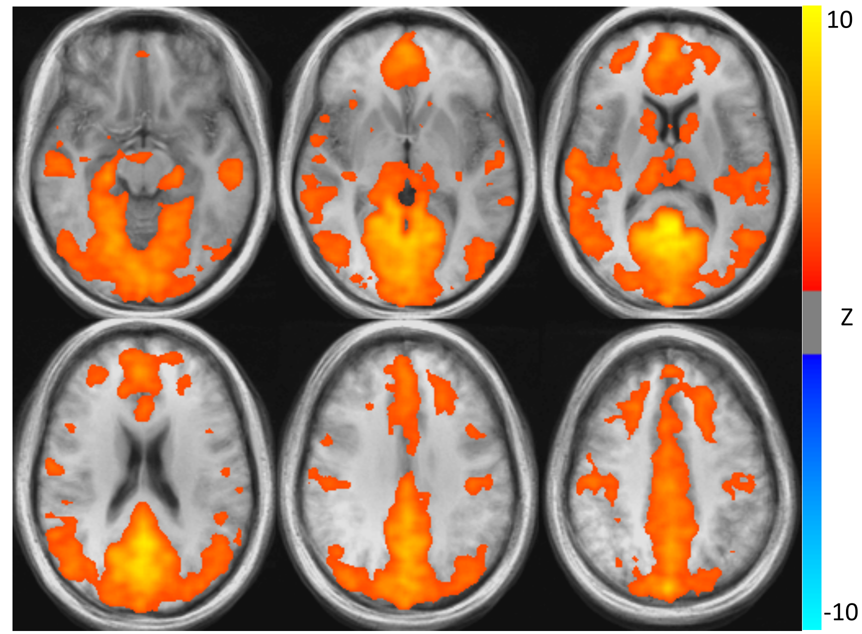


At best respiration and cardiac pulsation adds noise to regional connections. At worst it obscures neural connections.

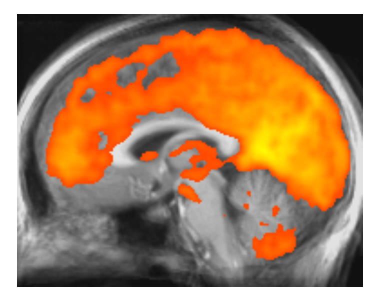
Respiration changes using RVT



Correlation (of PCC) at Rest



Group (n=10)

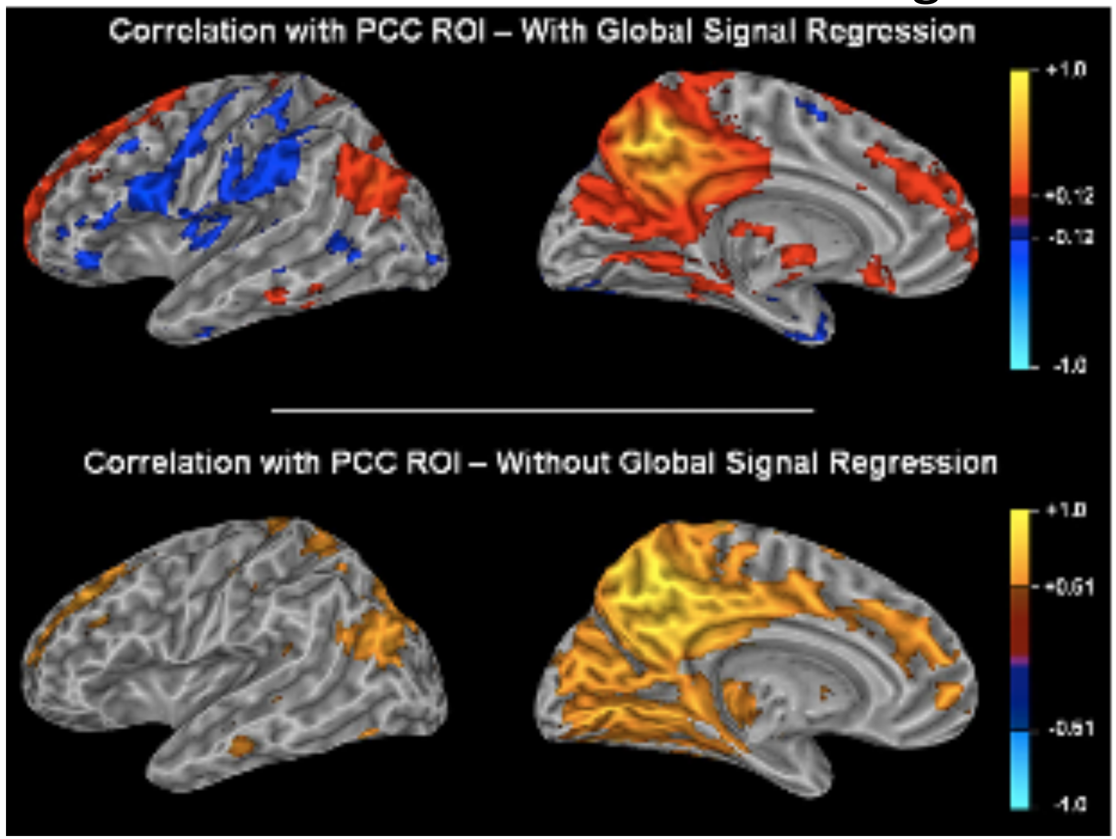


RVT = measuring and tracing (Respiration Volume)/time and removing it from the time series

Slide from Rasmus Birn

Anticorrelated networks are largely an artifact of a preprocessing decision

Correlations to the Posterior Cingulate

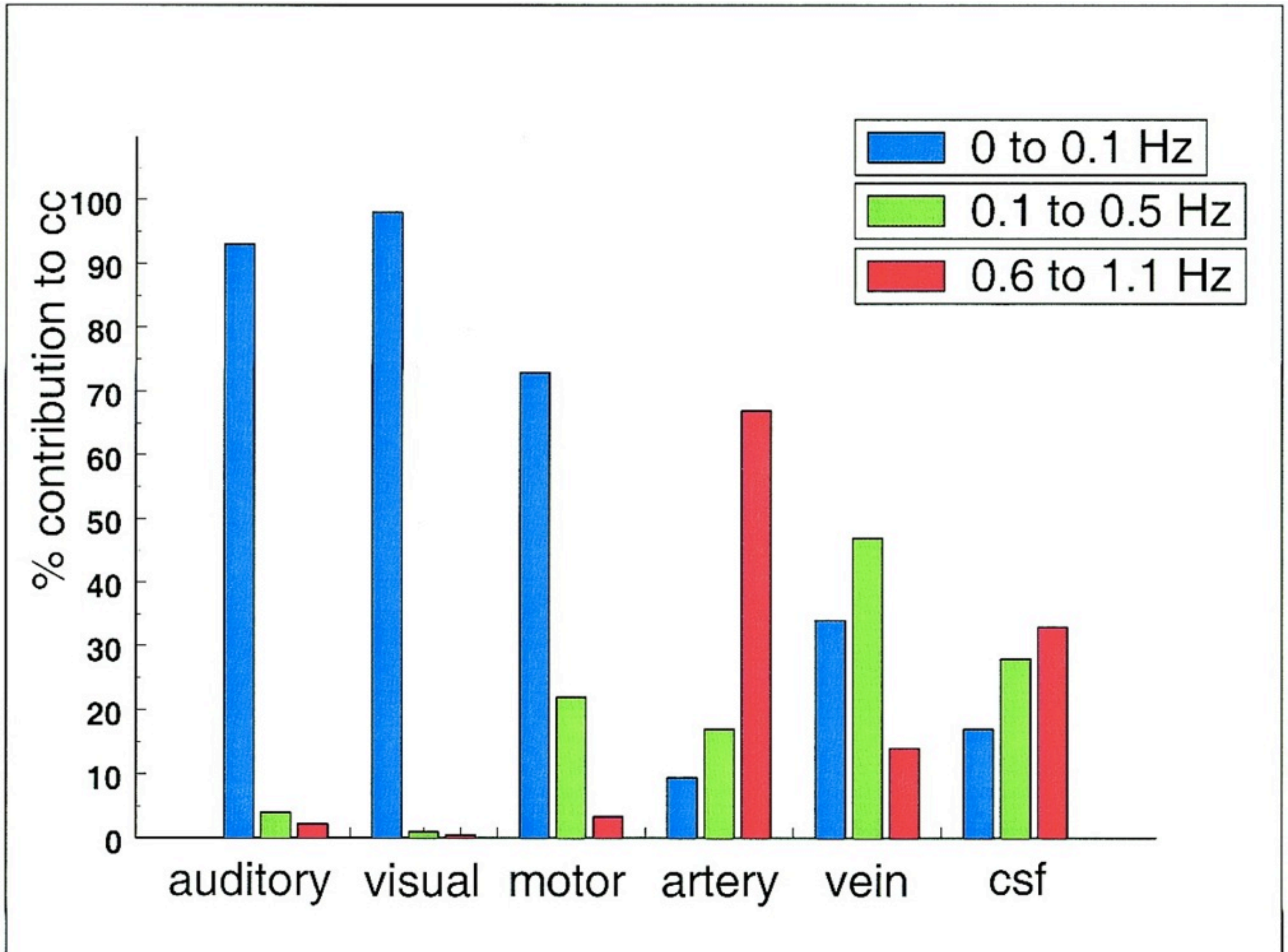


Murphy et al Neuroimage 2009

Removing the global signal was supposed to remove non-neural fluctuations, but it also induces anti-correlations

Removing uncharacterized signals can cause uncharacterized population differences

How do we know the remaining stuff is neural? Focusing on the low frequencies



Low frequencies dominate the correlation magnitudes for seeds in the cortex

Anything faster than a hemodynamic (0.3Hz) response is assumed to not be neural

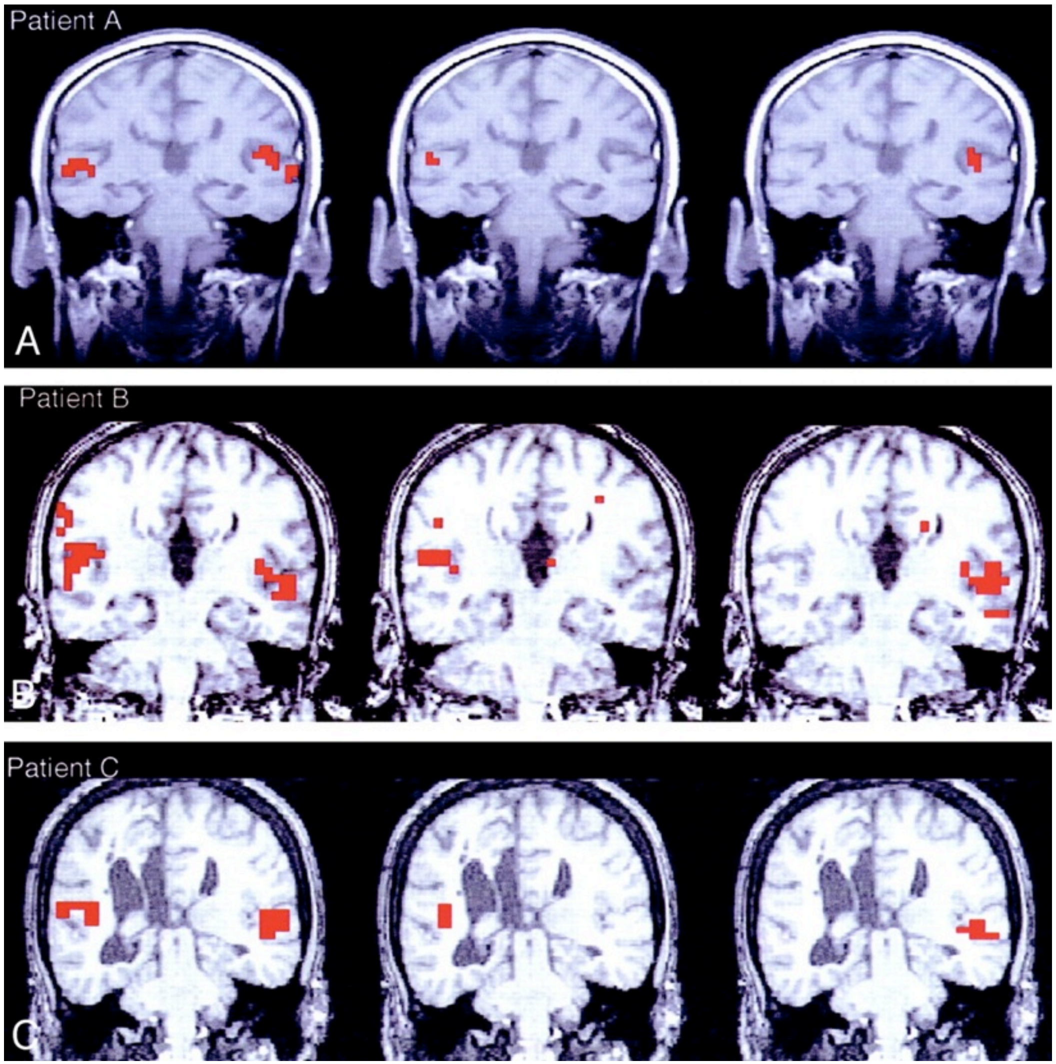
Cordes et al Am J Neuroradiol 2001

Based on a slide from M Lowe

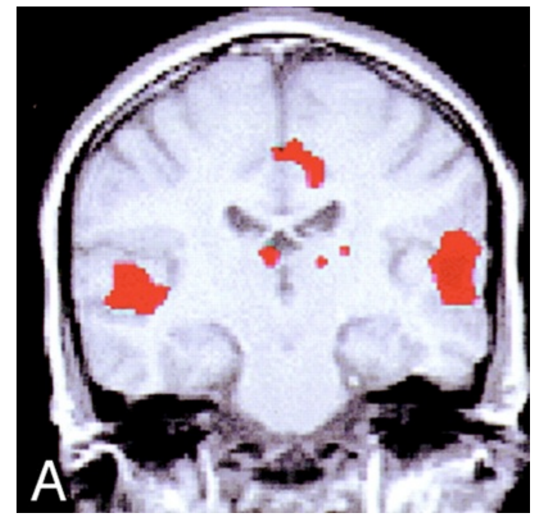
Agenesis of the corpus callosum

Activation from a text listening task

Right and left auditory seeds in resting data



Connectivity map from a healthy volunteer

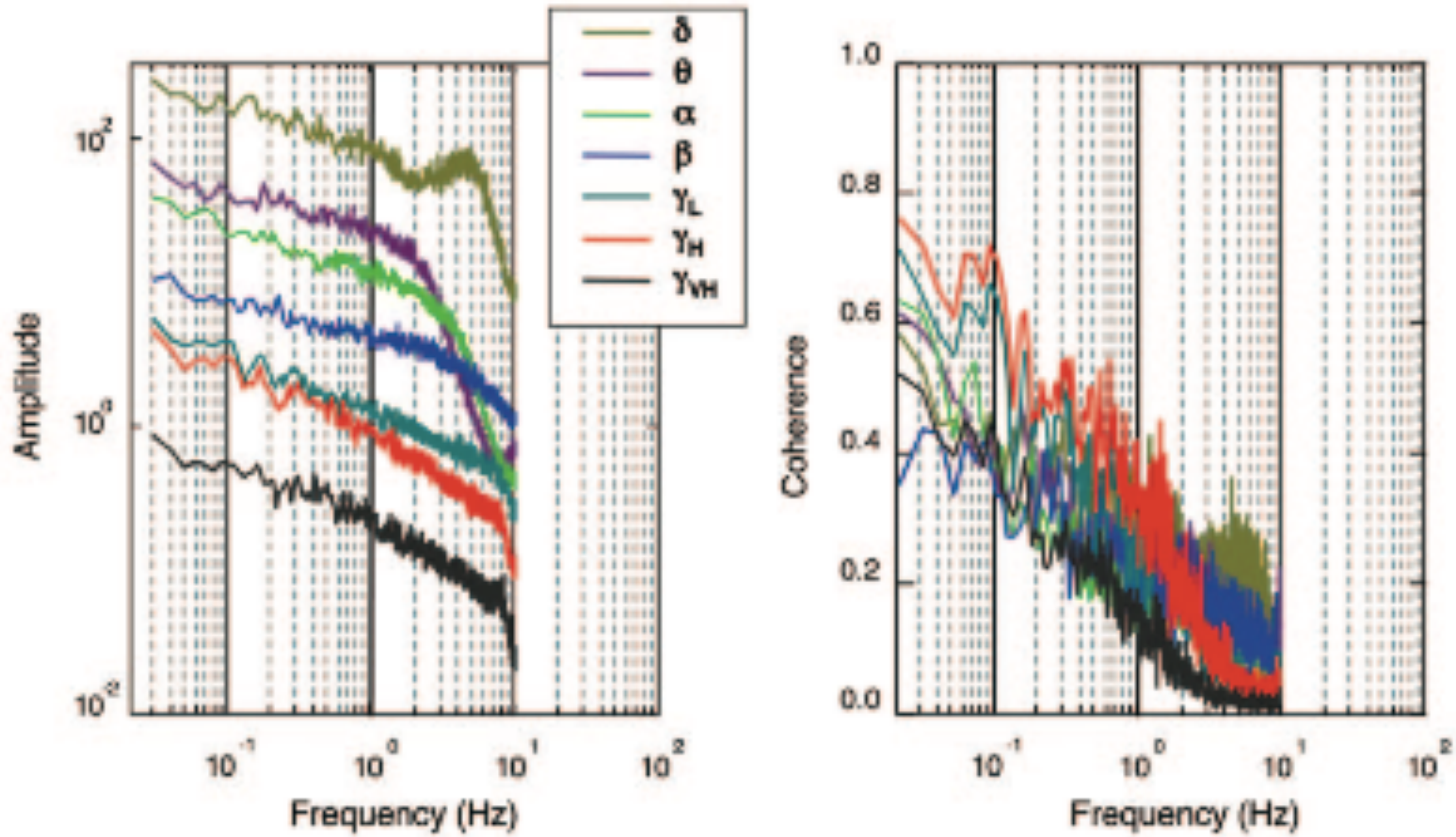


Quigley et al AJNR 2003

An acallosal patient was first presented by Lowe et al Neuroimage 9:S422 1999

Vasculature is still symmetric, but bilateral neurons are not connected

Electrical Signals can also be slow

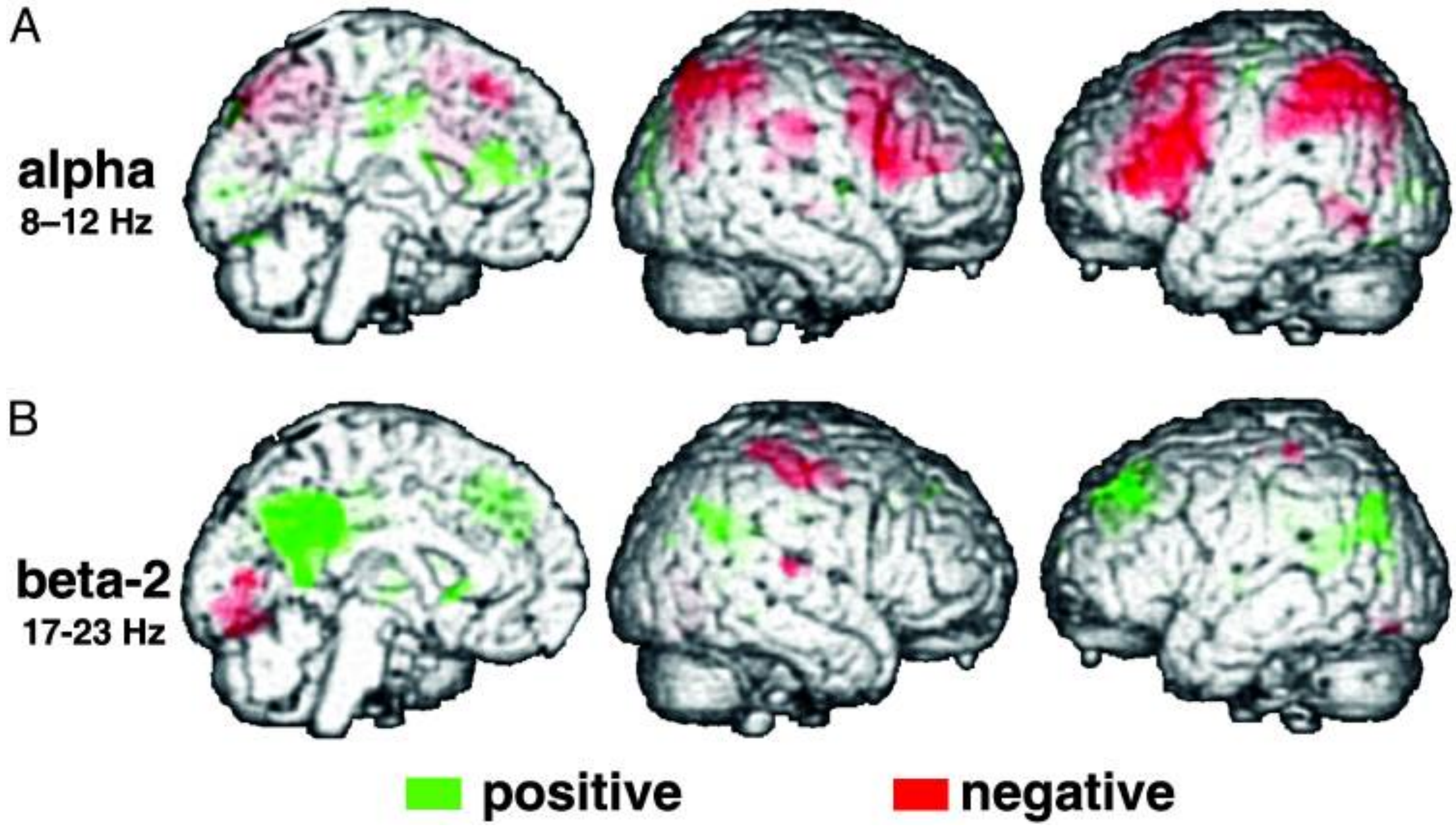


There is a high power signal and a coherence across electrodes in multiple LFP frequency bands.

Leopold et al Cerebral Cortex 2003

Based on a slide from M Lowe

Relationship to EEG

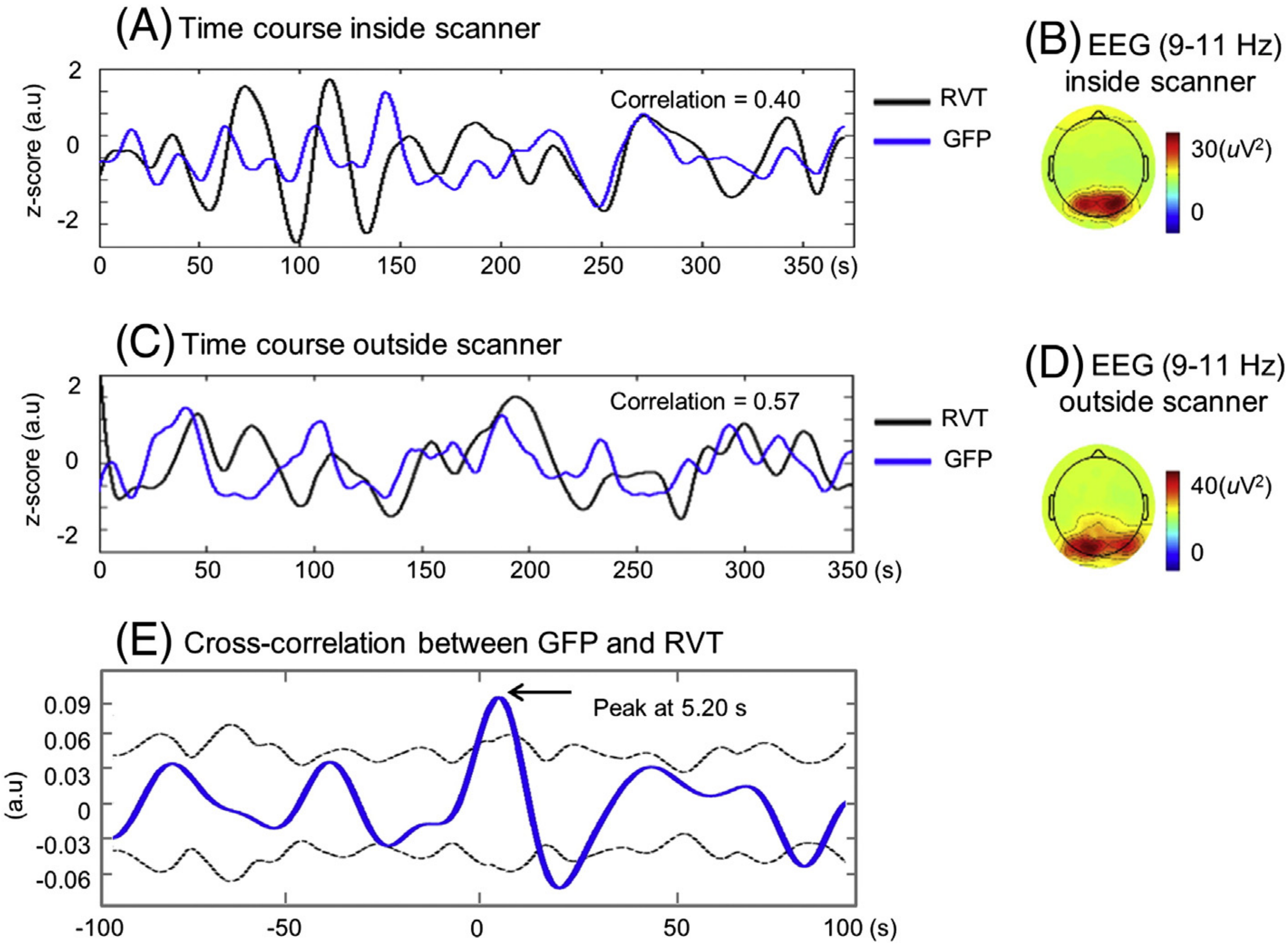


Activation and deactivation maps of EEG signals convolved with a hemodynamic response

Laufs et al PNAS 2003

Catie Chang will talk more about EEG/fMRI

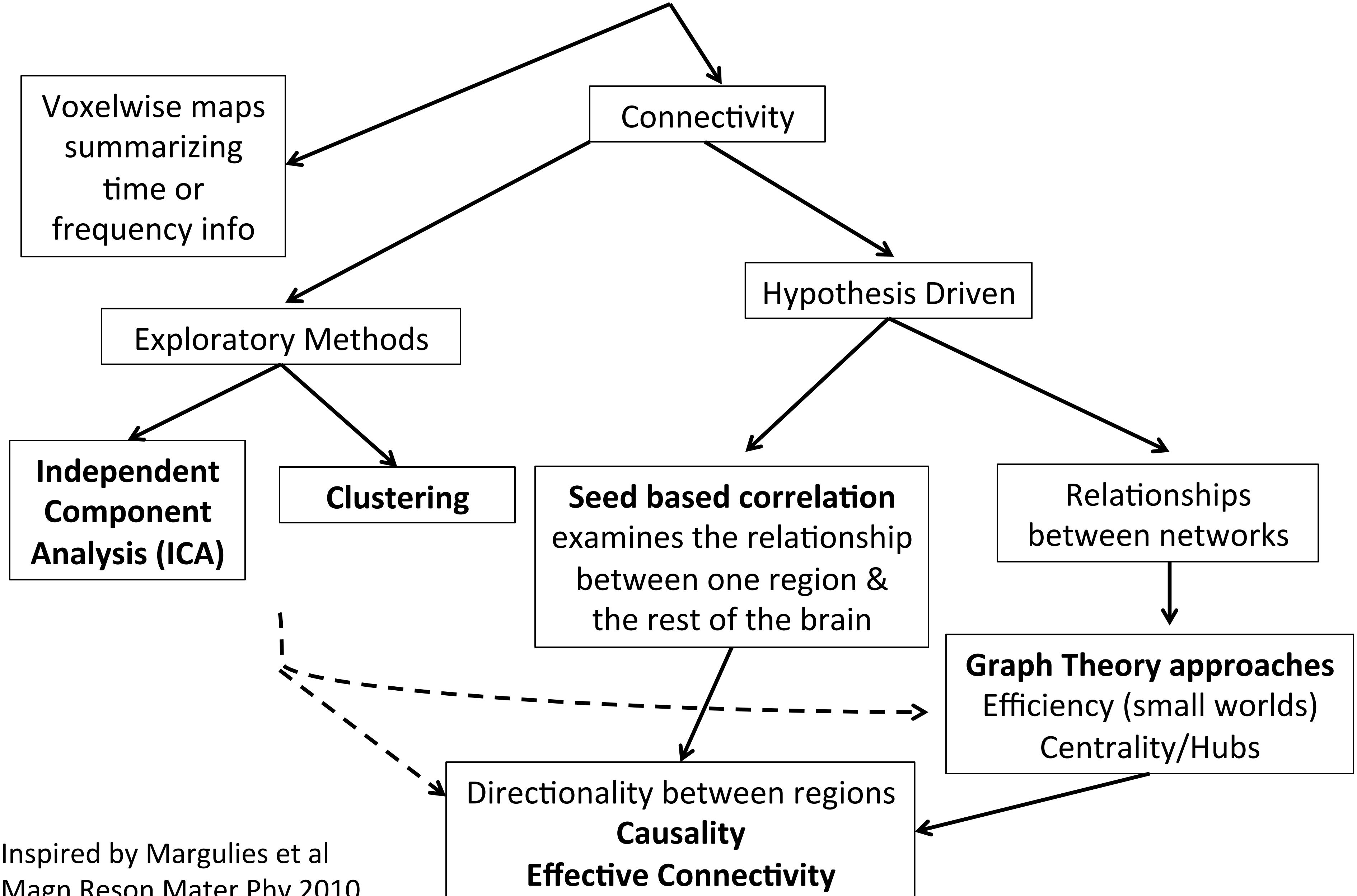
The EEG/fMRI rest relationship isn't simple



EEG alpha (GFP) also correlates with breathing (RVT)

Yuan, Zotev, Phillips, Bodurka
Neuroimage, 2013

We have our rest fMRI data. Now what?



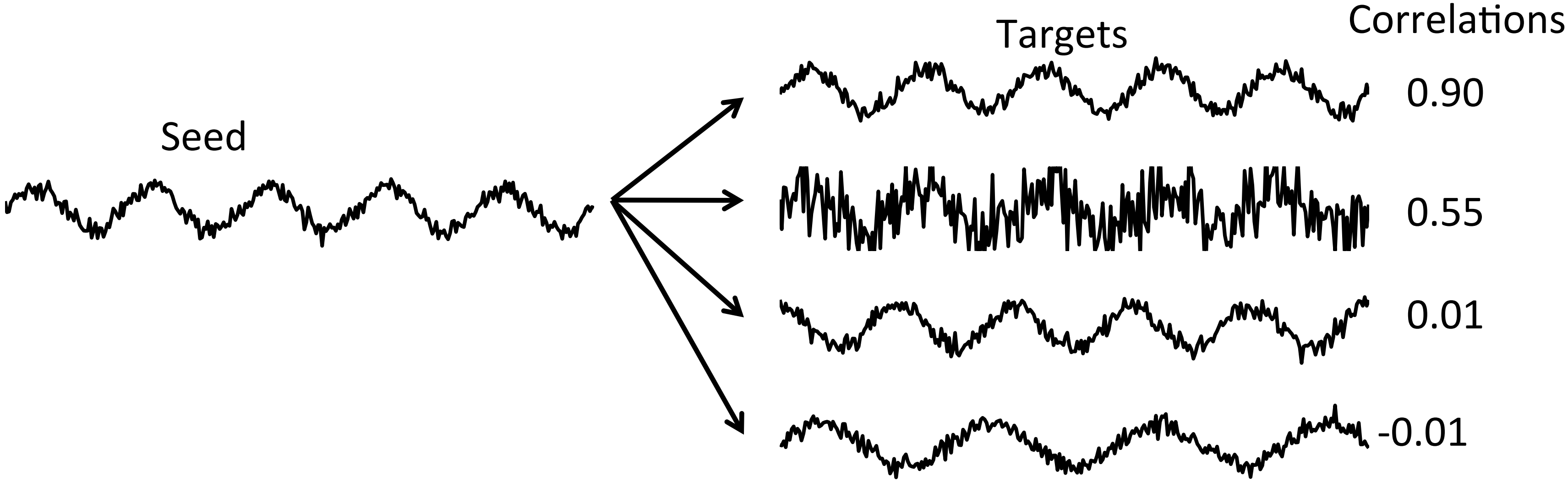
Inspired by Margulies et al
Magn Reson Mater Phy 2010

Methods

At best these methods give us pretty maps of regions that we know have commonalities

- What is normal variation?
- Preprocessing matters
- What differences are statistically significant?
- What differences are reliable and stable across methods?

Connectivity Analysis tools
Seed Based Methods

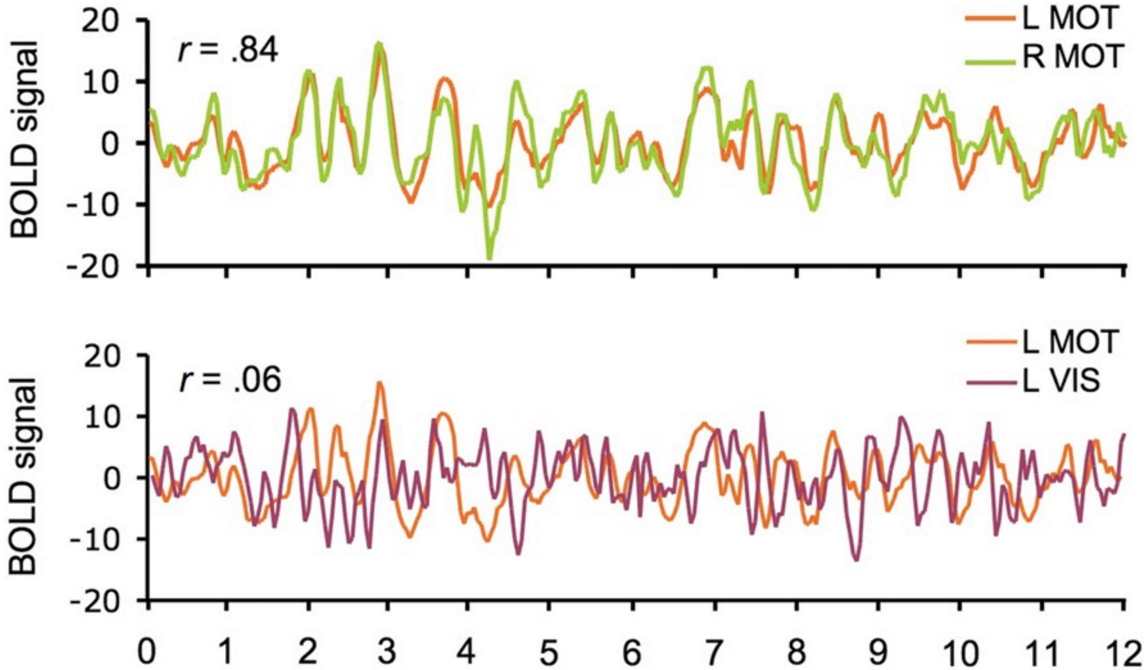


Find voxels with that have similar X to the seed

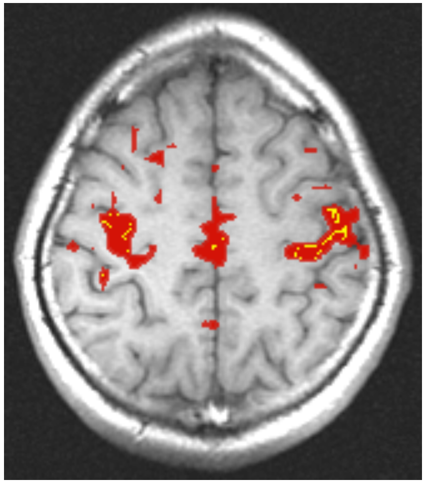
- Correlation — Time series shapes
- Coherence — Frequency characteristics
- Mutual Information — Nonlinear similarities
- Causality — Nonlinear similarities

Coherence, MI and Causality can also give directionality information (with unclear accuracy)

Seed Based Methods



Van Dijk J Neurophys 2010



***B. Biswal** et al., MRM, 34:537 (1995)*

Advantages of using seeds

- **Hypothesis Driven**
  Answers potentially relevant questions:
  - What regions are correlated with the seed region?
  - How do correlations with the seed region change across populations or after an intervention?
- Shown to give fairly reliable and scientifically relevant results
- Conceptually simple and computationally fast (almost instant in AFNI)

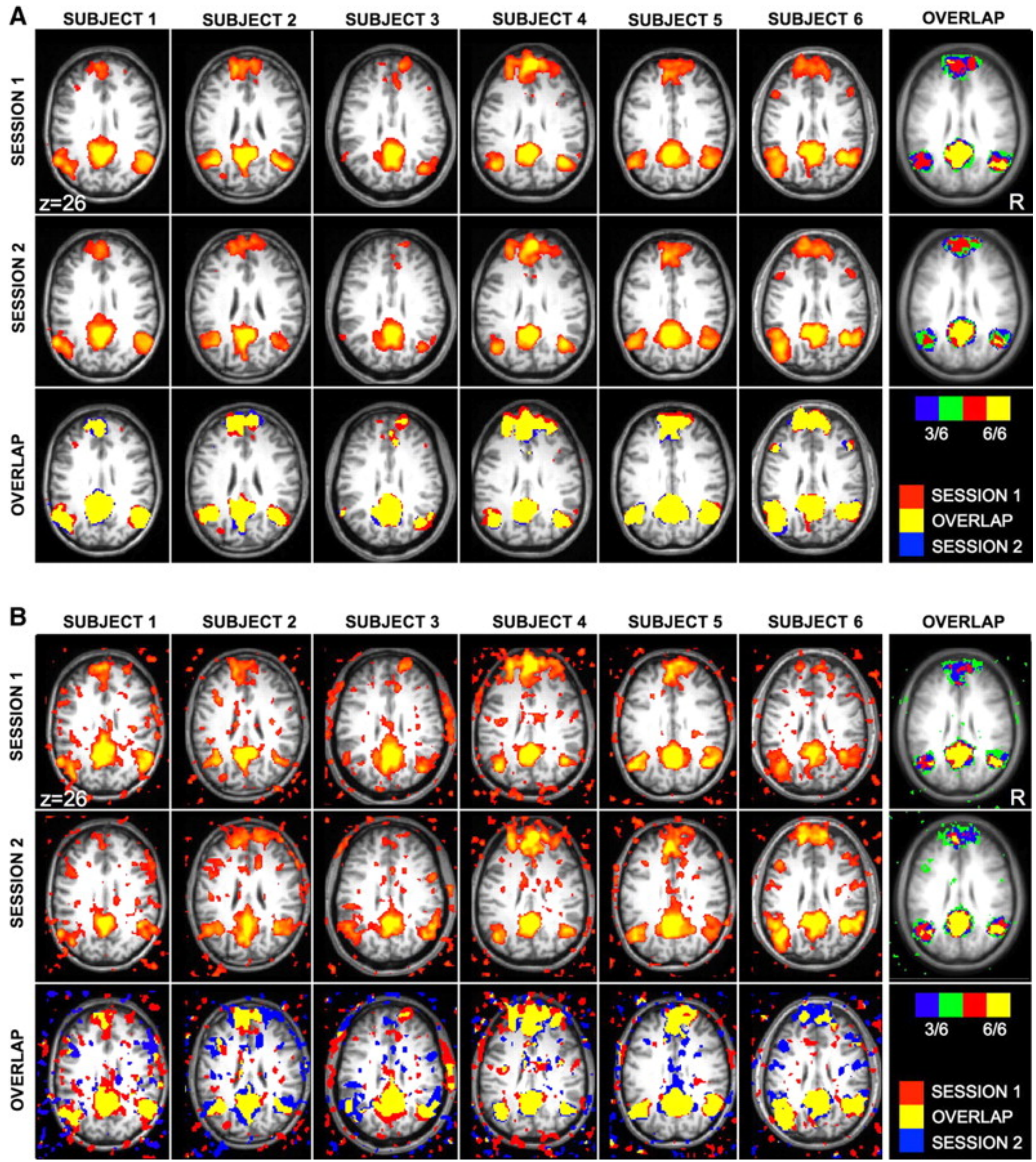
Cross subject and Session Reliability

20 minute sessions

5 minute sessions

Catie Chang's talk will show that things aren't quite this simple

Van Dijk J Neurophys 2010



Seed based group analysis

One fairly standard method

Take the correlation value map from each subject, convert statistics to z scores and calculate voxelwise group statistics

Issues to consider

Spatial normalization

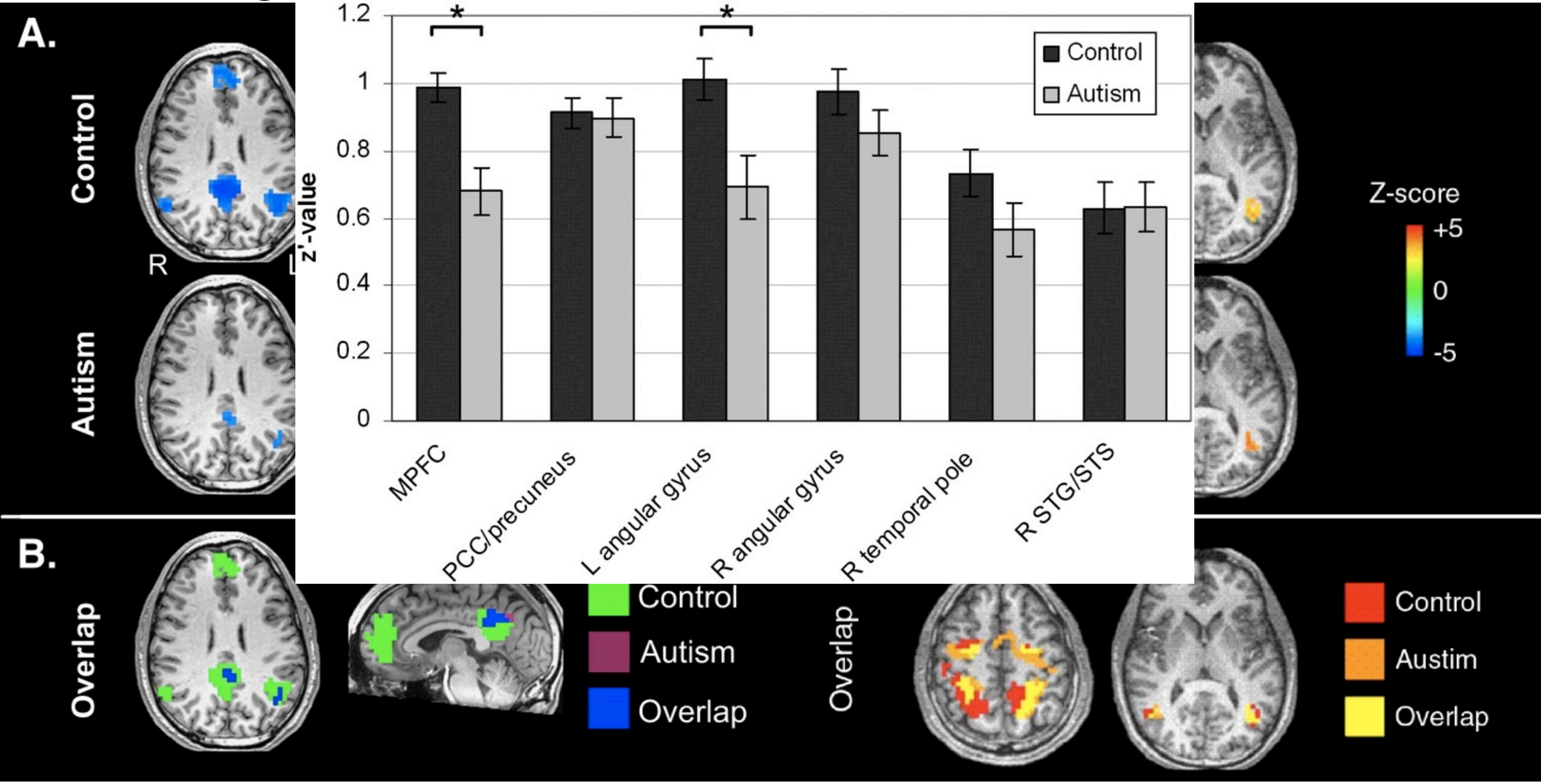
Consistent seed region selection

Watch out for outlier data

Network changes with Autism

"Task Negative" Network

"Task Positive" Network

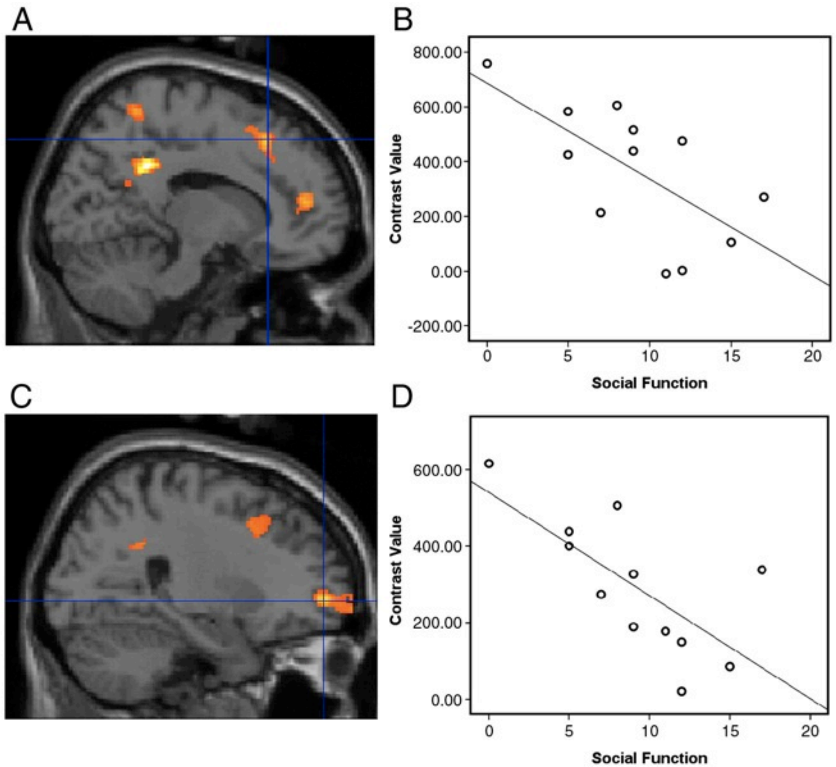


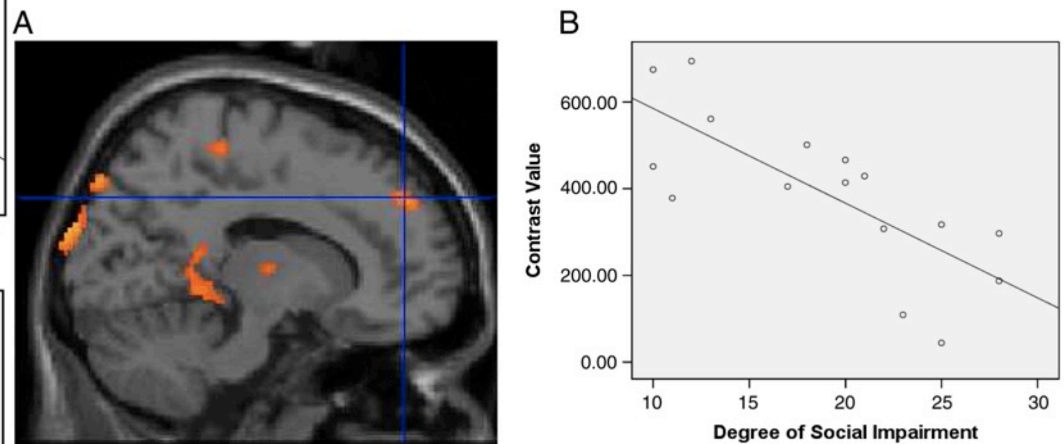
Kennedy & Courchesne Neuroimage 2008

Connectivity linked to Autistic behavior

Adults

Adolescents





Monk, Peltier, et al,
Neuroimage 2009

Weng, Wiggins, et al,
Brain Research, 2010

Significant relationships in the Superior frontal gyrus

(Analysis Circularity warning)

Results are sensitive to processing steps

Data set	Pipeline: Seed selection from	Pipeline: Task effects & temporal filtering *	Pipeline: Field of view *	FC results (p<.05, corr.): Under-conn. voxels	FC results: Over-conn. voxels	FC results: Under-connectivity ratio †	Overall pattern
RSVP	TD activation	Task-activated/HP	Whole Brain	3563	132	0.93	Underconnected
			ROIs only	21	0	1.00	Underconnected
		Task-regressed/BP	Whole Brain	708	798	-0.06	Mixed
	ASD activation	Task-activated/HP	Whole Brain	2073	176	0.84	Underconnected
			ROIs only	5	3	0.25	Mostly underconnected
		Task-regressed/BP	Whole Brain	603	1078	-0.28	Mostly overconnected
	Combined activation	Task-activated/HP	Whole Brain	3711	127	0.93	Underconnected
			ROIs only	14	0	1.00	Underconnected
		Task-regressed /BP	Whole Brain	696	833	-0.09	Mixed
	Just et al.	Task-regressed/ BP	Whole Brain	745	976	-0.13	Mixed
VS	TD activation	Task-activated/HP	Whole Brain	376	2580	-0.75	Overconnected
			ROIs only	29	0	1.00	Underconnected
		Task-regressed/BP	Whole Brain	467	934	-0.33	Mostly overconnected
	ASD activation	Task-activated/HP	Whole Brain	308	3704	-0.85	Overconnected
			ROIs only	3	2	0.20	Mixed
		Task-regressed/BP	Whole Brain	518	2012	-0.59	Overconnected
	Combined activation	Task-activated/HP	Whole Brain	323	2519	-0.77	Overconnected
			ROIs only	17	2	0.79	Underconnected
		Task-regressed /BP	Whole Brain	442	1334	-0.50	Overconnected
	Just et al.	Task-regressed/ BP	Whole Brain	87	1900	-0.91	Overconnected
RS	DMN	HP	Whole Brain	1076	771	0.17	Mixed
			ROIs only	57	1	0.97	Underconnected
	DMN	BP	Whole Brain	1403	1076	0.13	Mixed
	Just et al.	BP	Whole Brain	301	2106	-0.75	Overconnected

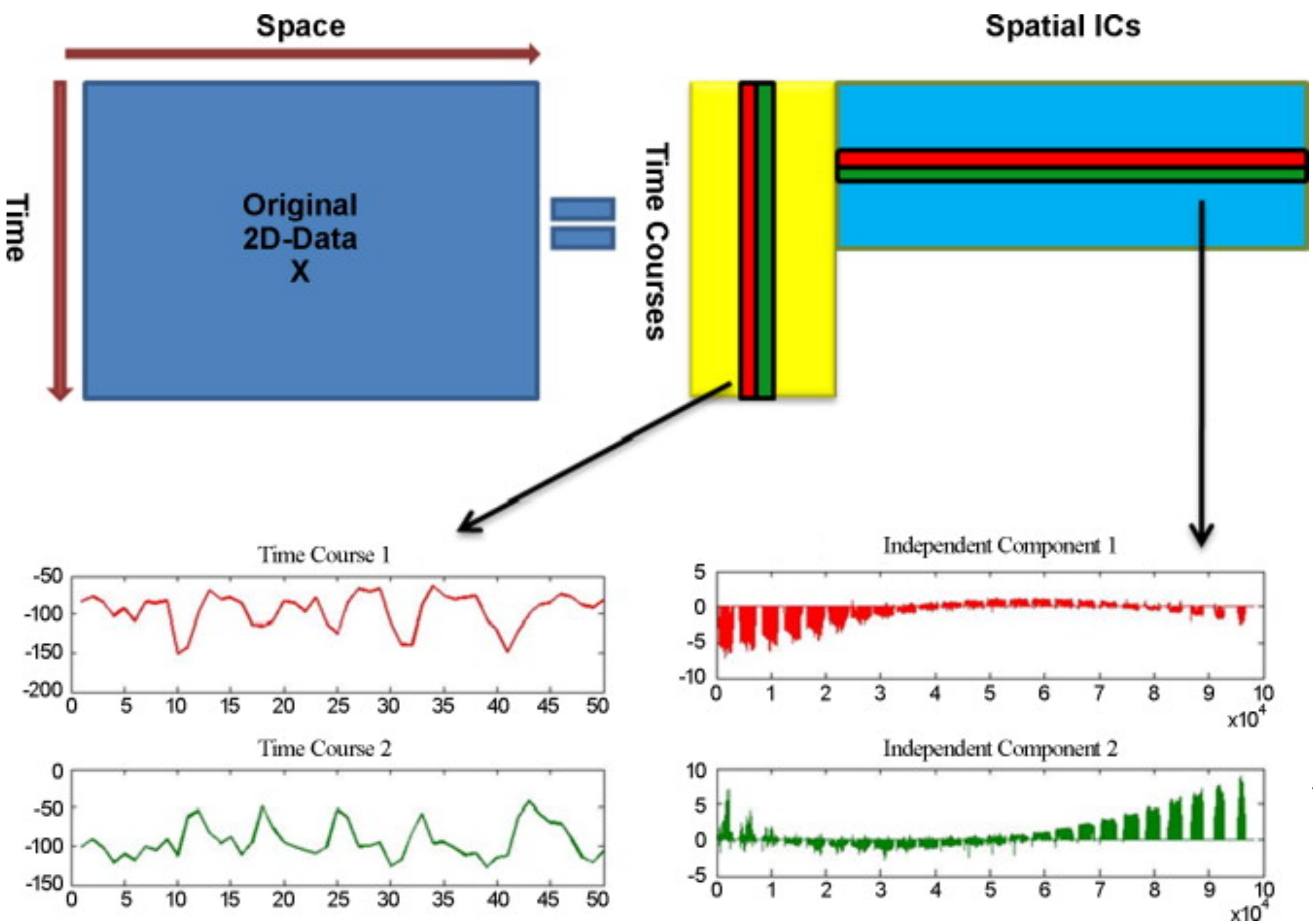
Mueller, R.A., et al Resting State Conference 2012

Disadvantages of using seeds

- Potentially sensitive to seed selection and pre-processing
- After pre-processing, no easy way to distinguish neural from non-neural connections
- Needs a separate seed for every network
- We still don't know what differences are scientifically or clinically meaningful

Independent Component Analysis

Great for identifying common patterns without making model assumptions or even selecting regions of interest



Data is decomposed into a set of spatially independent maps and a set of time courses

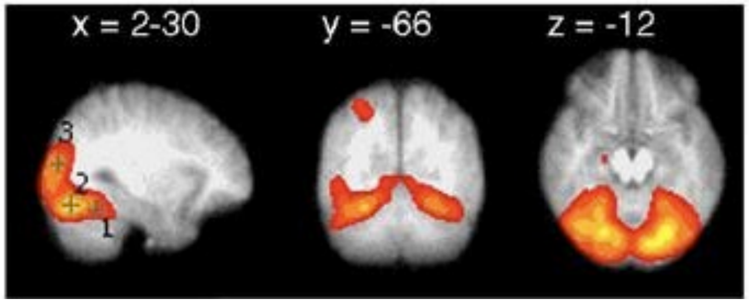
There are multiple methods for identifying relevant components

Also multiple ways to model groups of volunteers

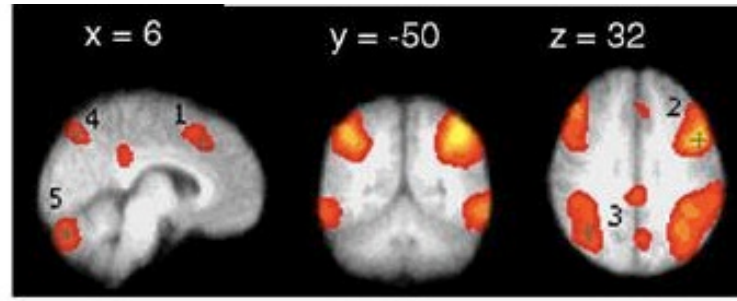
Li et al Computerized Medical Imaging and Graphics March 2009

5 brain networks using ICA

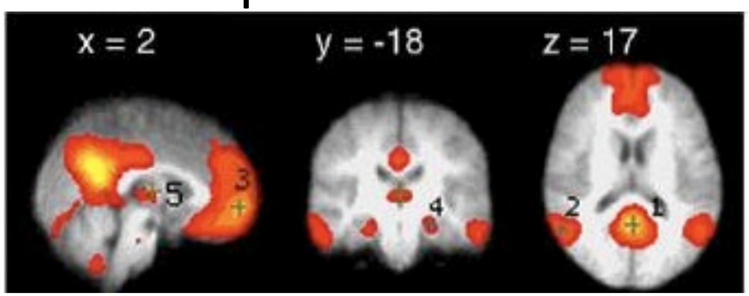
Visual



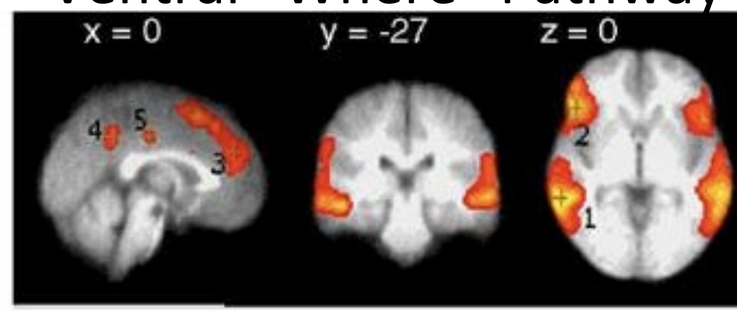
Dorsal "What" Pathway



Visuospatial & Executive

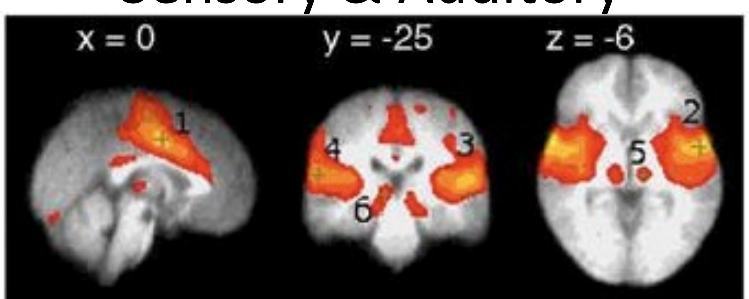


Ventral "Where" Pathway



M. De Luca et al., *NeuroImage* 2006

Sensory & Auditory

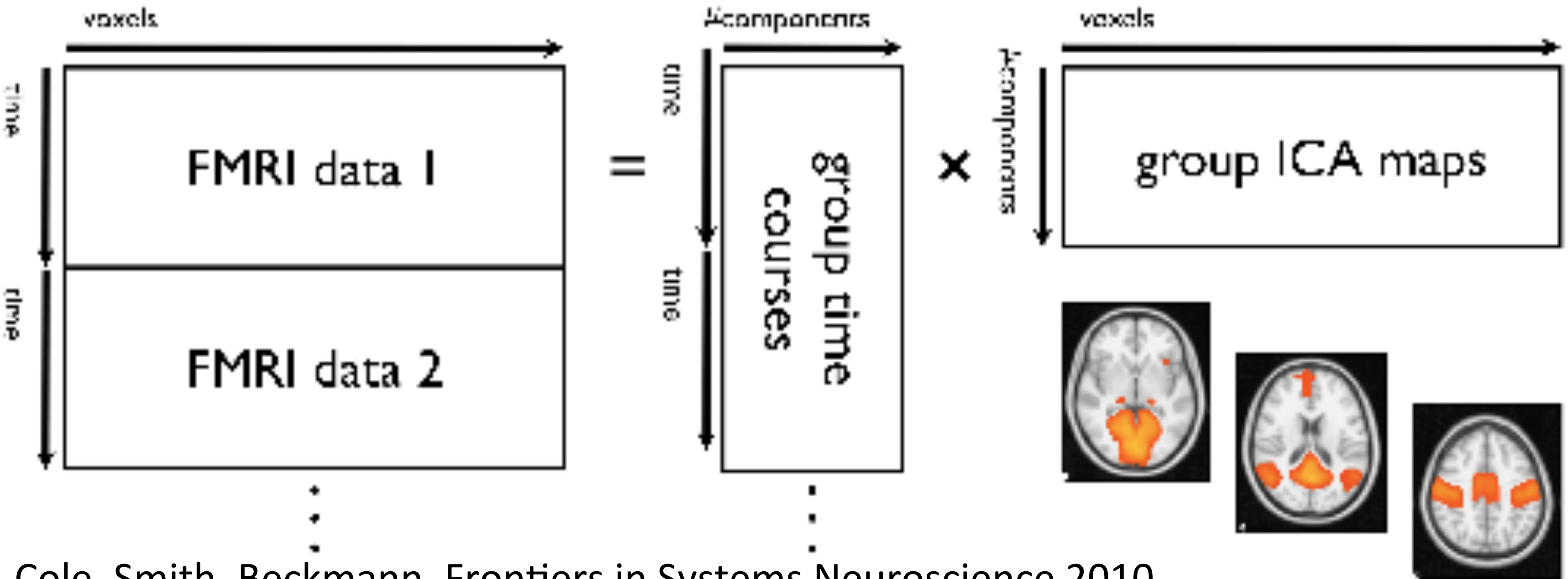


Network names are based on knowledge from past research

ICA Advantages

- No seed regions
- Everything in the brain is placed in a network
- Can often pull out equipment, respiration and motion artifacts as separate components
  (at least for individual subject ICA)
- Can start without any model of what you expect to see
- Can find something interesting you weren't looking for
- Can be used for noise removal before running other analyses

One ICA Group Analysis Method



Cole, Smith, Beckmann, Frontiers in Systems Neuroscience 2010

Model the subjects' data as one long time series

The component time series from each subject can also be used to generate subject-specific maps and magnitude values

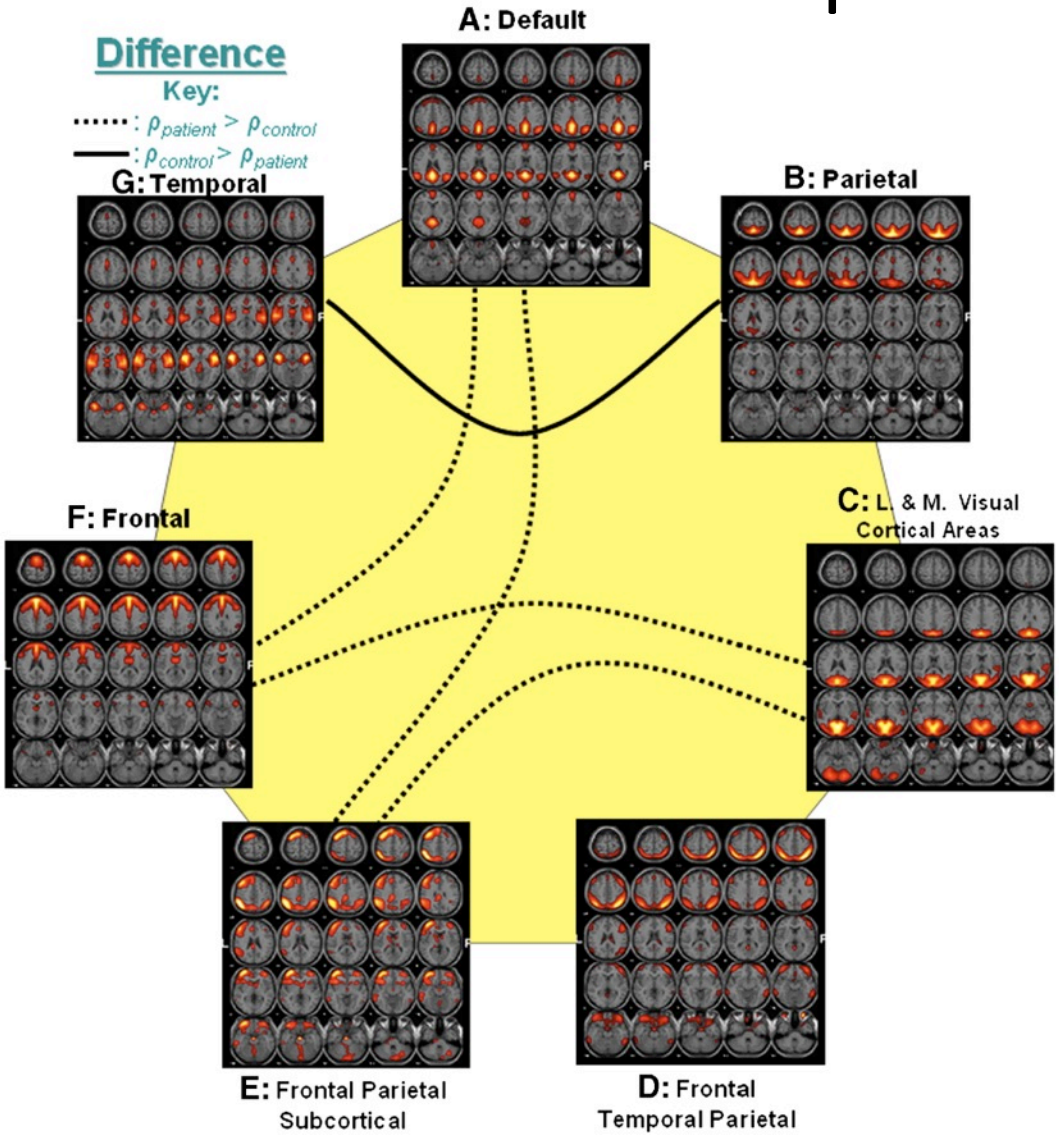
There are other ICA Group analysis methods

For example you can run ICA on each subject and find ways to align components

gRAICAR Yang et al, Neuroimage 2012

For any approach you still need assumptions of components of interest or use the component times series or spatial maps to identify interesting similarities or differences across groups

ICA then causality to show differences in Schizophrenia



Identified the same components in the two populations

Looked at how the different components correlated with each other at various lags

Correlations between networks differed between healthy volunteers and patients

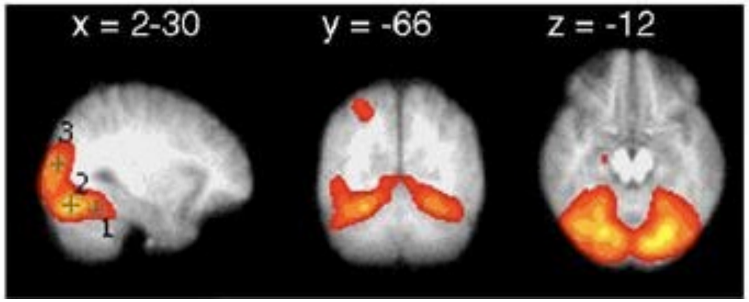
Jafri et al Neuroimage 2007

Limitations of ICA

- All we know is that components are independent
  - What the #$%! does that mean?
- While we might observe consistency across a population it isn’t a mathematical requirement
- You need to define the # of components & this affects the results
- Calculations are iterative and can vary even with the same data
- There is no order to the components. You always need to set rules on how to identify relevant components and significant voxels

5 brain networks using ICA?

Visual



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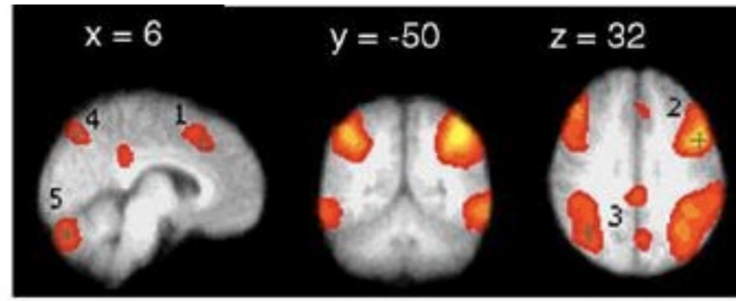
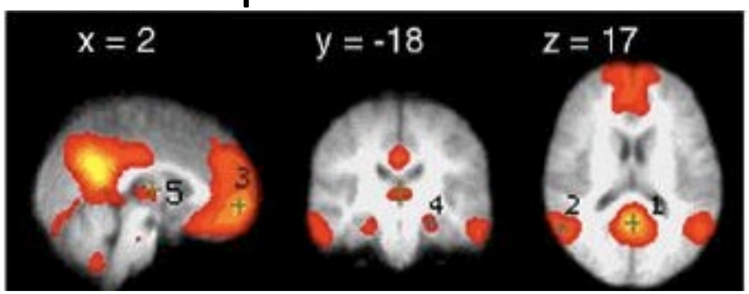


Visuospatial & Executive



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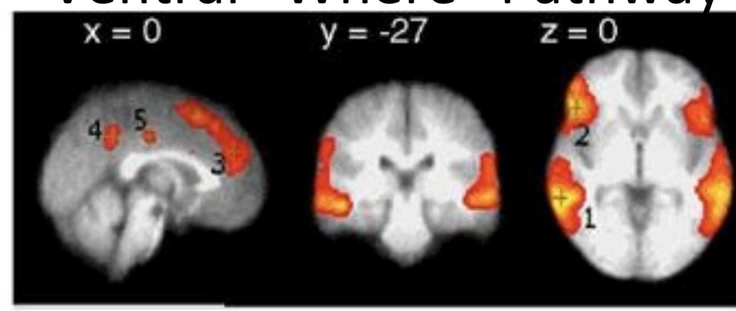
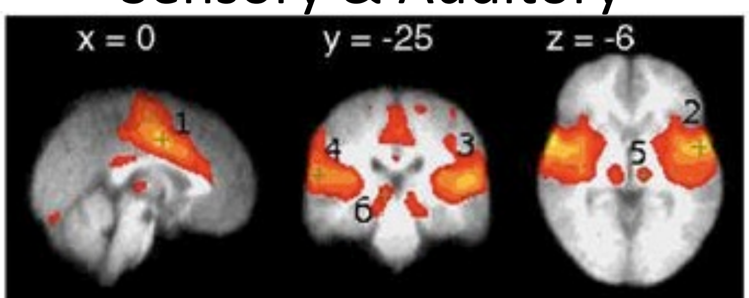
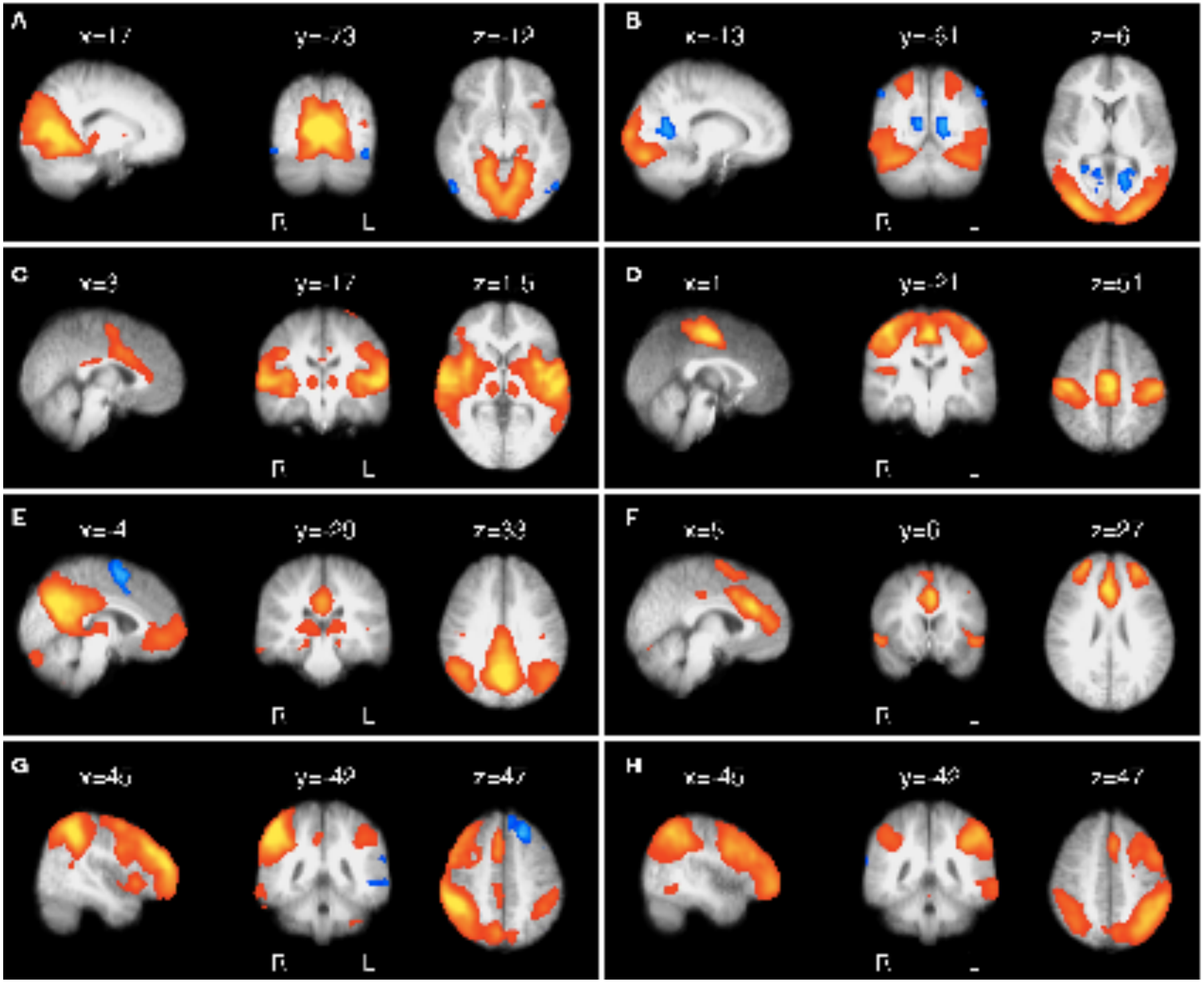


M. De Luca et al., *NeuroImage* 2006

Sensory & Auditory

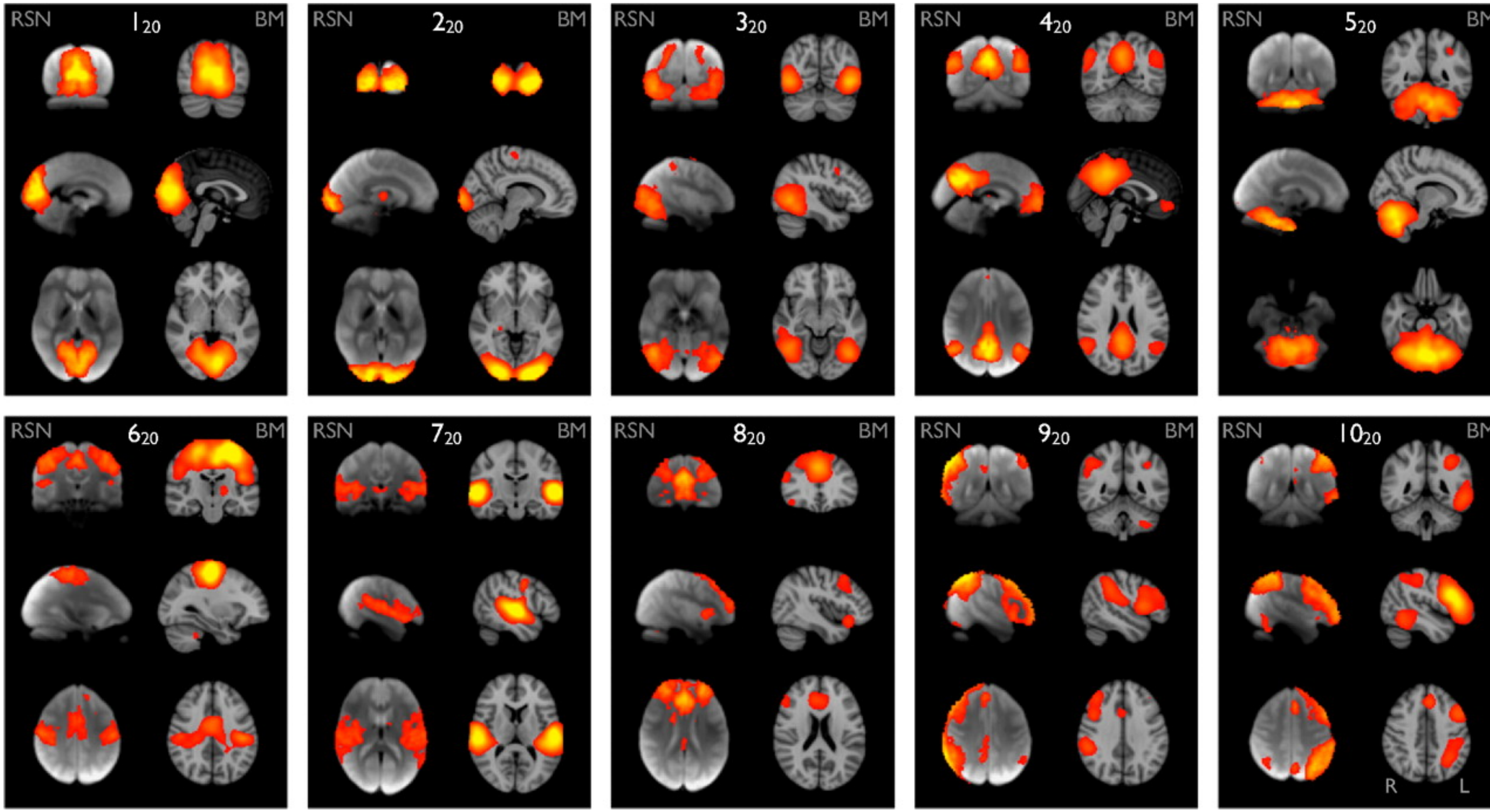


8 Brain networks using ICA?



Beckman, De Luca, et al, Philos Trans R Soc Lond, B, Biol Sci, 2005

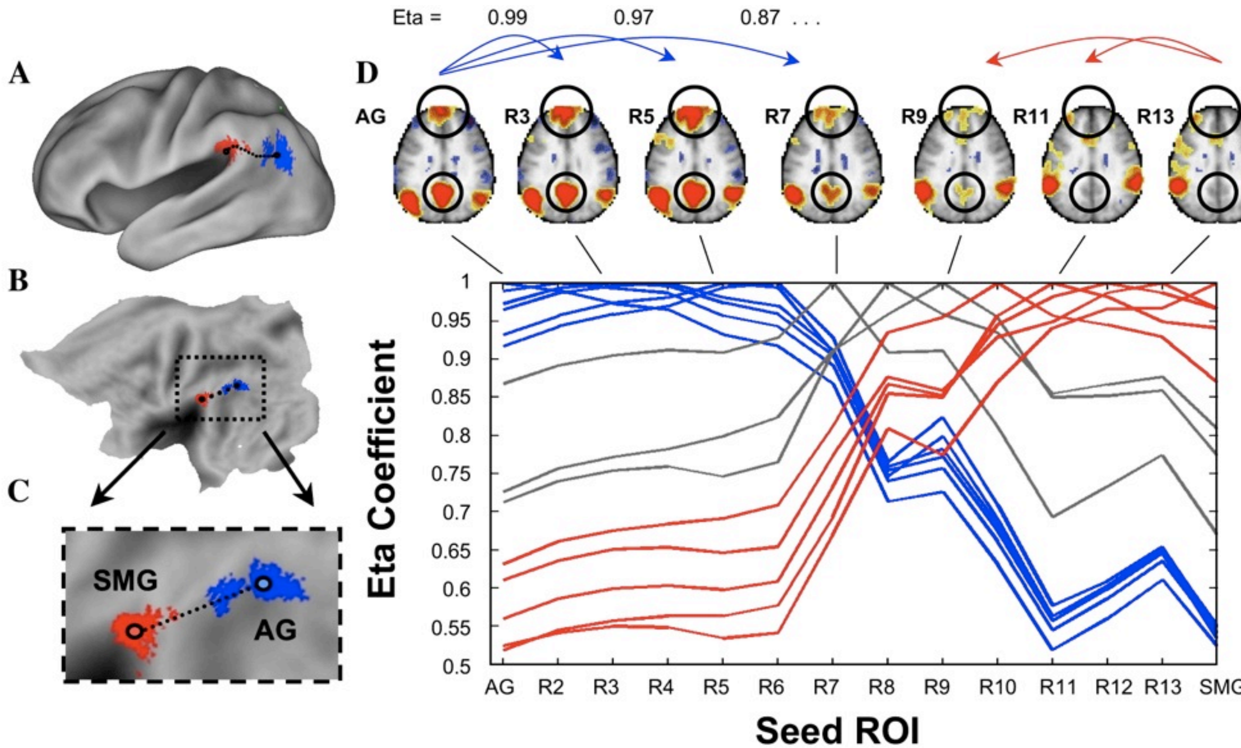
10 brain networks using ICA?

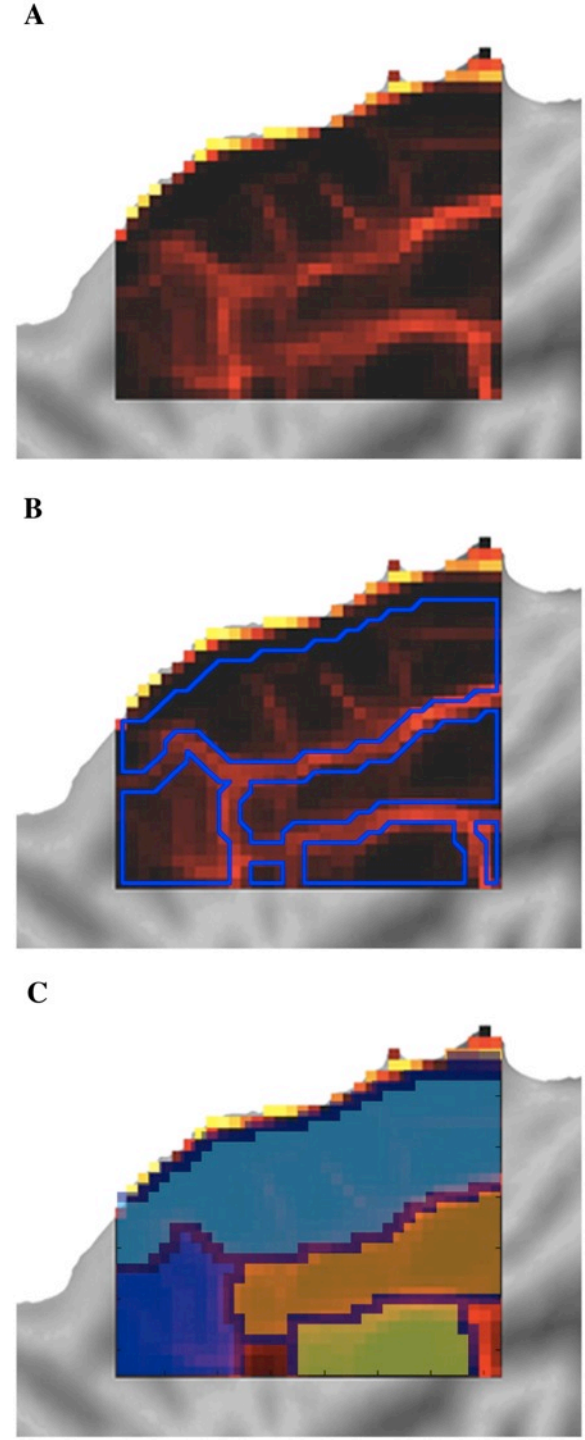


All these brain network counts are from the same respected lab!

Smith S M et al. PNAS 2009;106:13040-13045

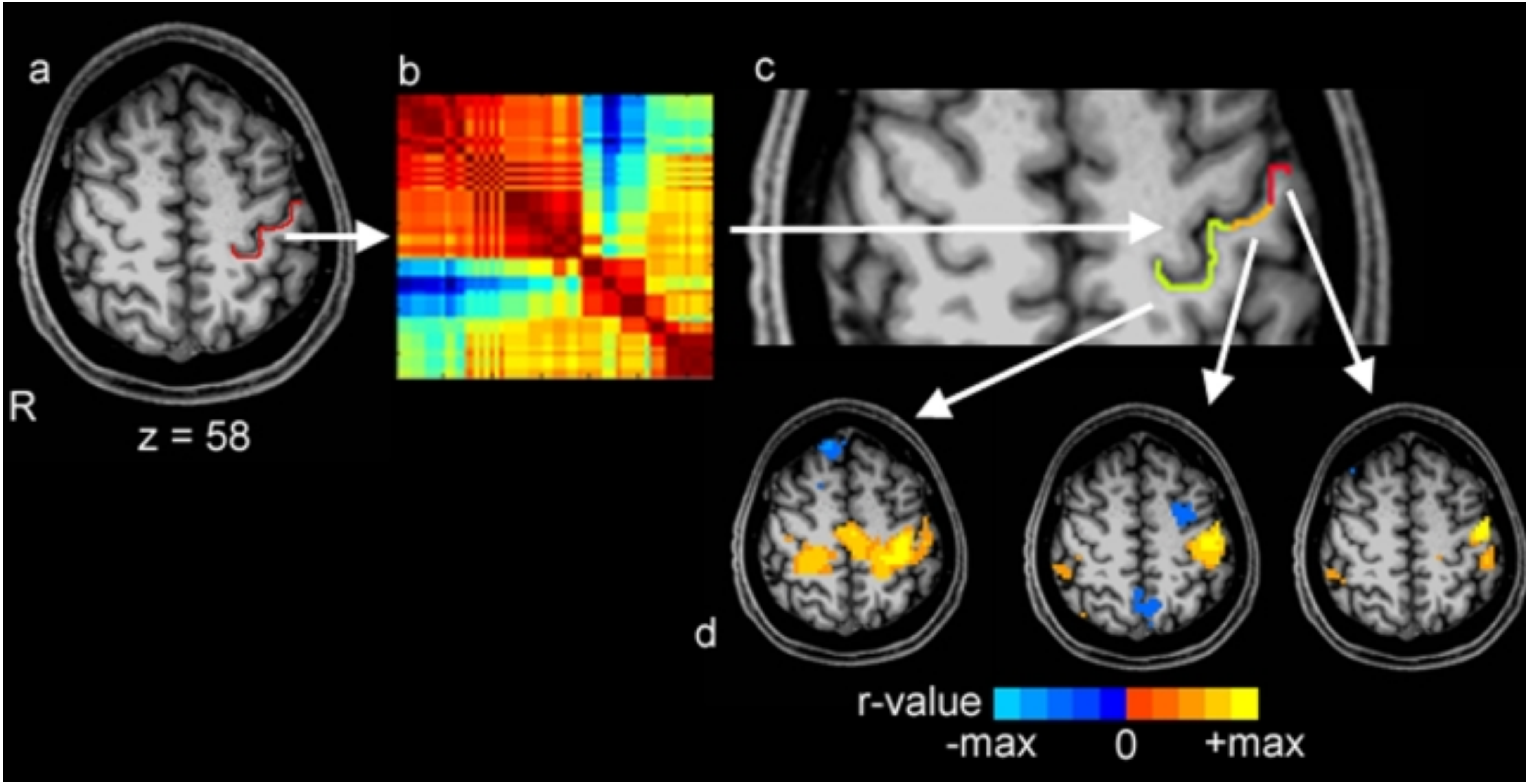
Clustering / Parcellation





Cohn et al Neuroimage 2008

Parcellation of the Postcentral Gyrus



Long, Margulies Villringer OHBM Meeting 2010

Clustering + & -

+ Potential for seeing clustering differences across populations

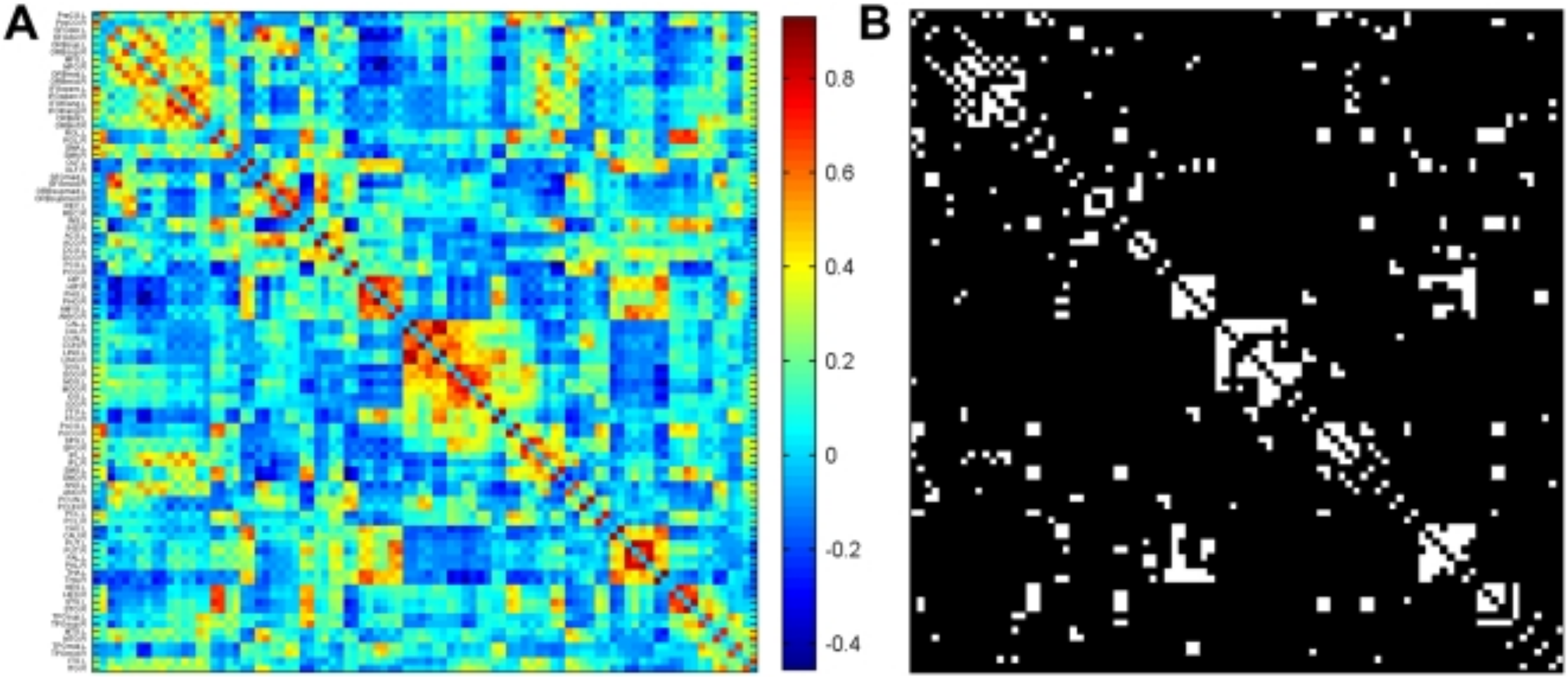
+ Useful for dividing brain by functional commonalities

+ Creates inputs to other analyses
  (cluster-based seeds)

- Some approaches are very sensitive
  to # of clusters requested

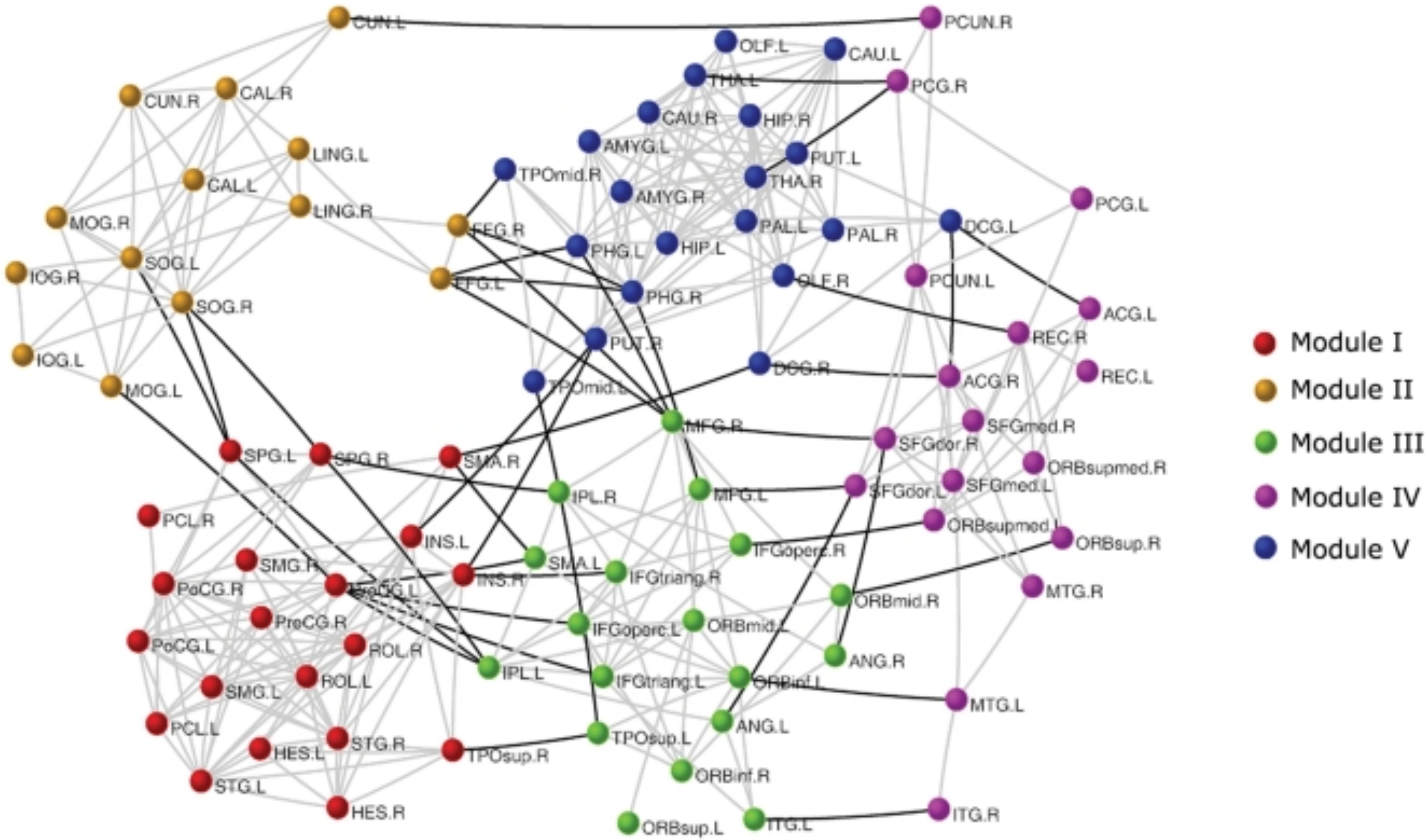
- You'll always get clusters whether or not they mean anything (no clear gold standard of accuracy)

Graph Theory Approaches



He et al PLOS ONE 2009

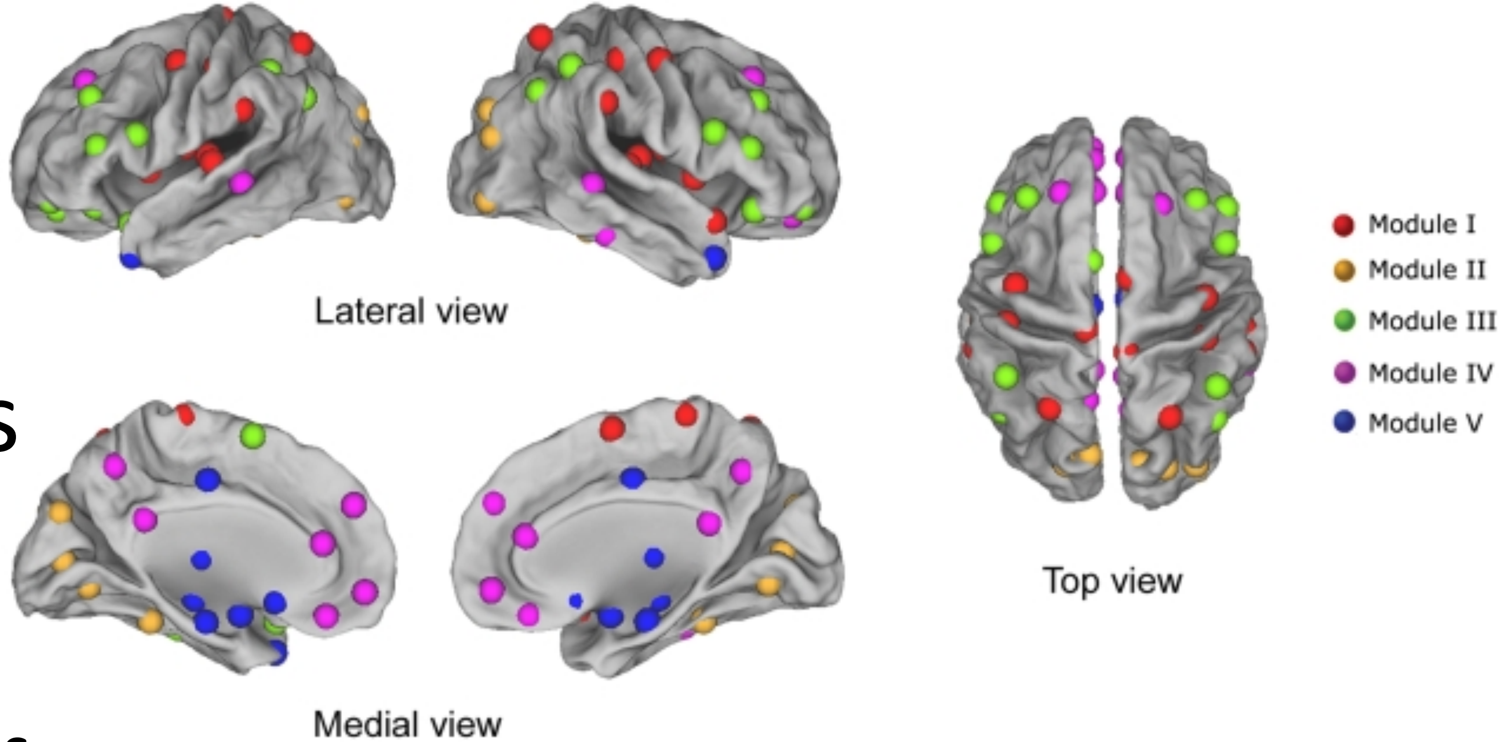
Modular Brain Networks



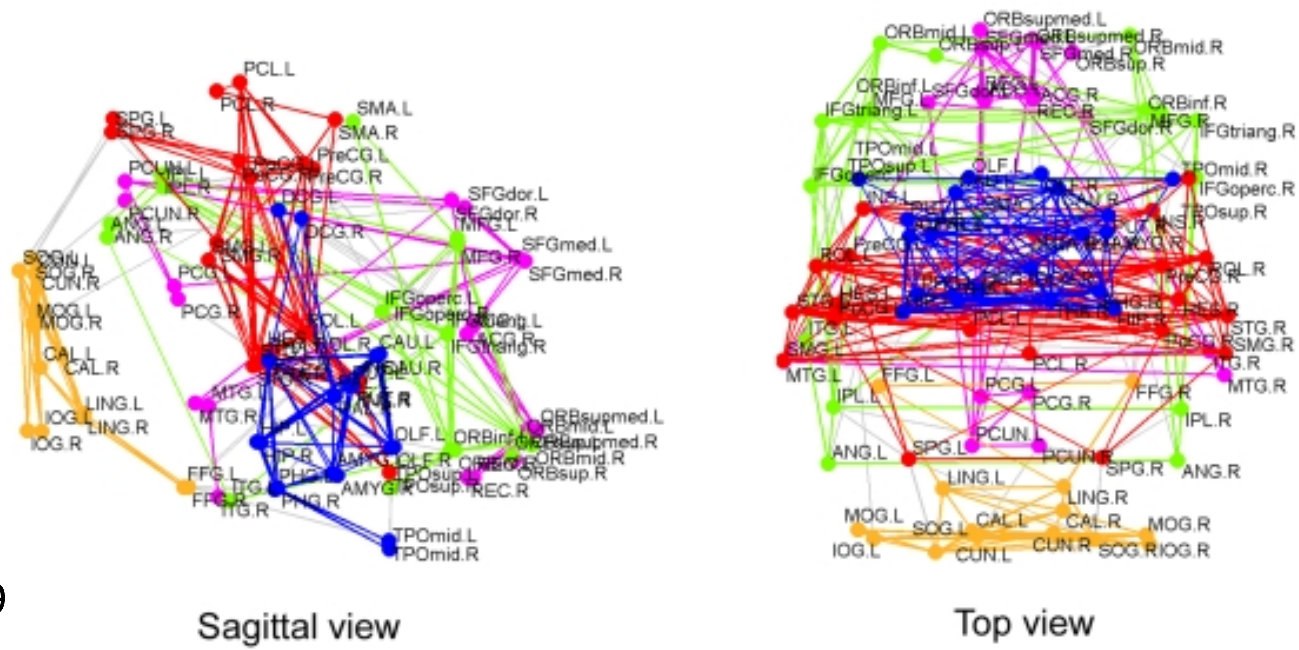
The closer the dots, the more similar their time series

He et al PLOS ONE 2009

Modular Brain Networks

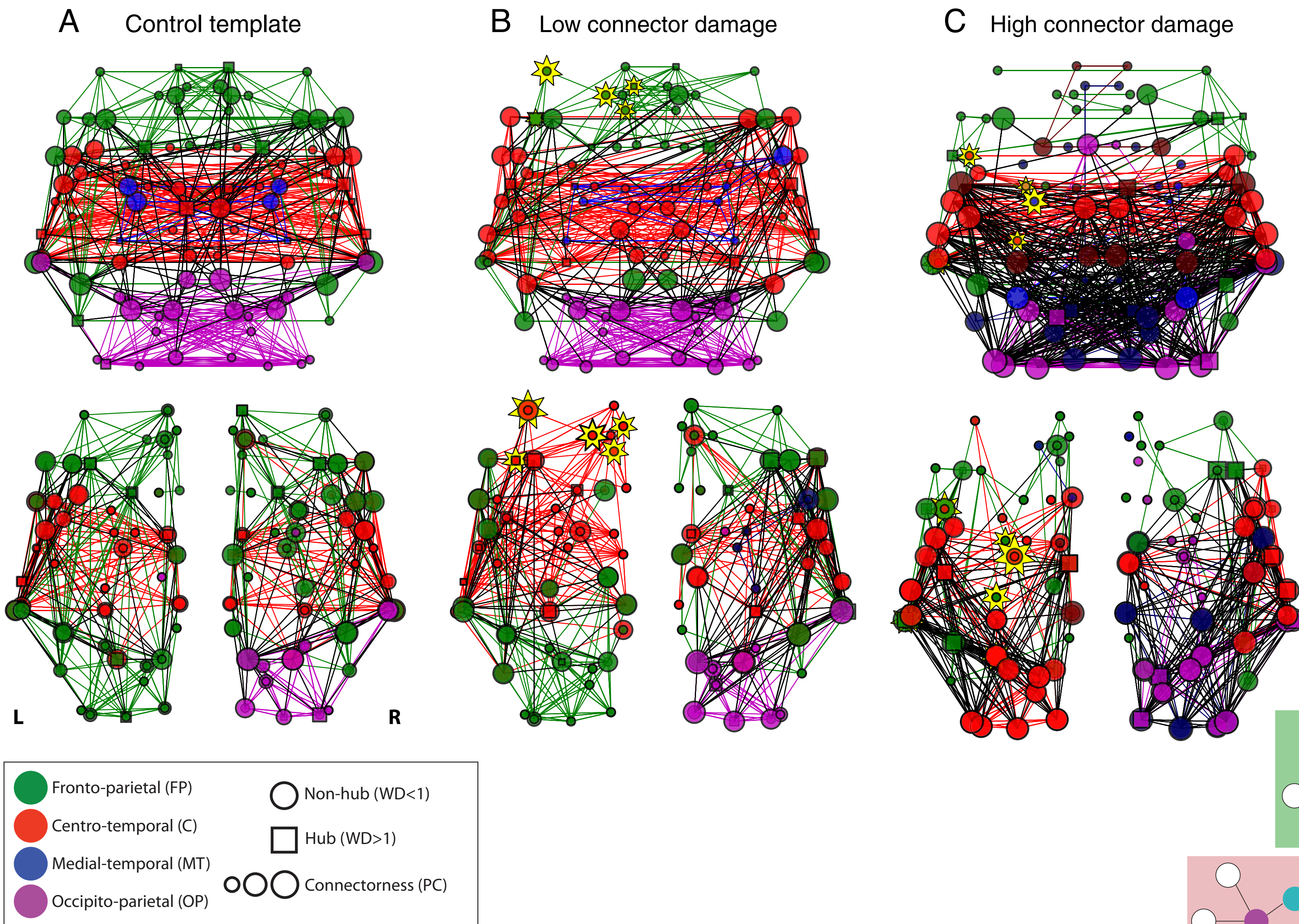


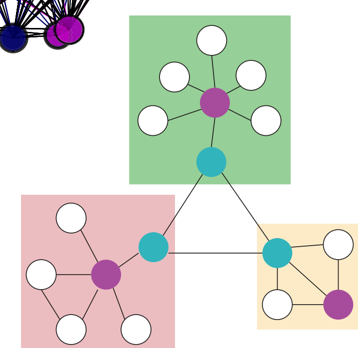
Same regions and connections as the last slide represented in brain-space



He et al PLOS ONE 2009

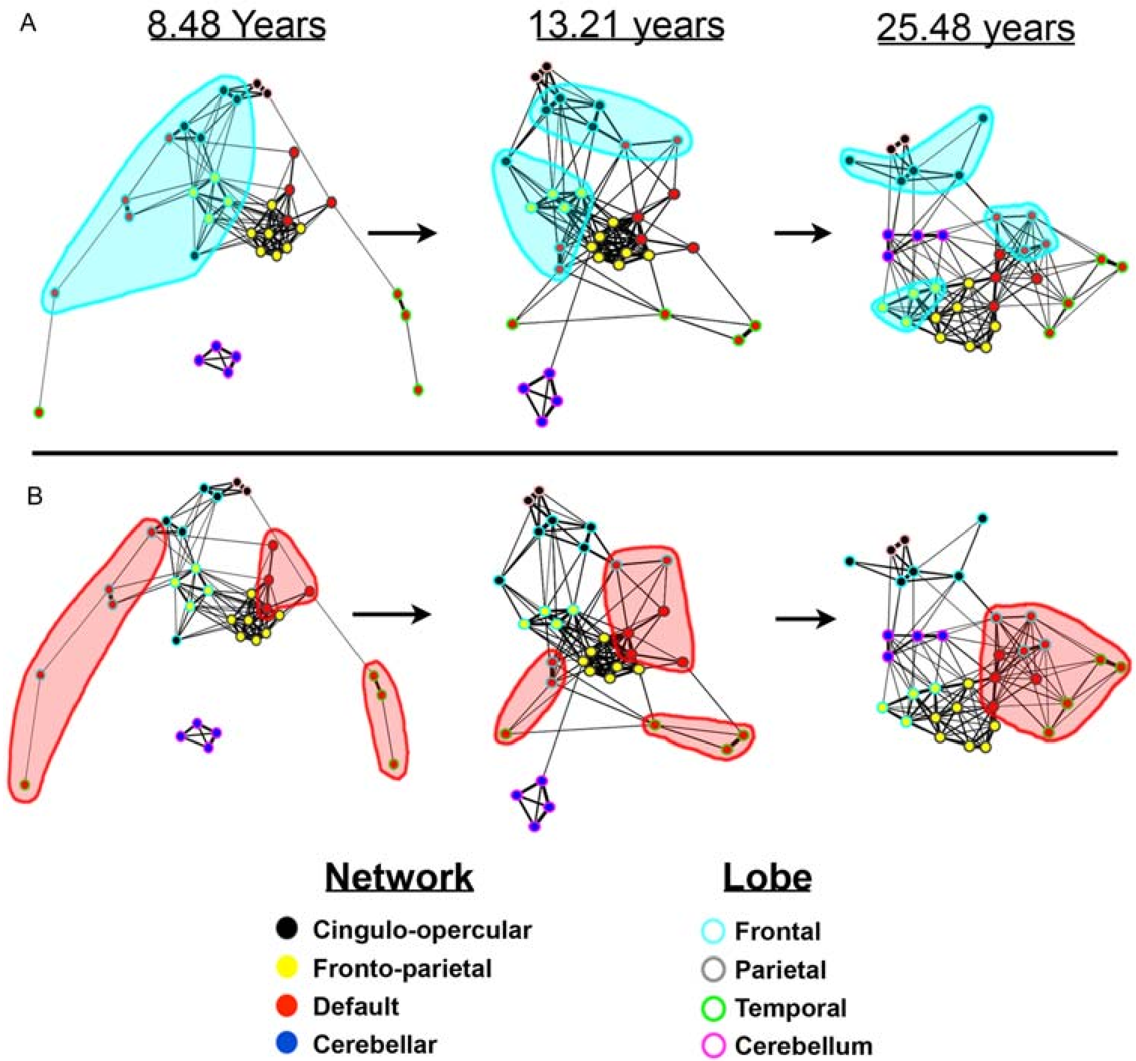
Network disruption depends on stroke lesion location





C Gratton, Nomura, Perez, D'Esposito J Cog Neuro, 2012

Functional Brain Networks Develop from a "Local to Distributed" Organization

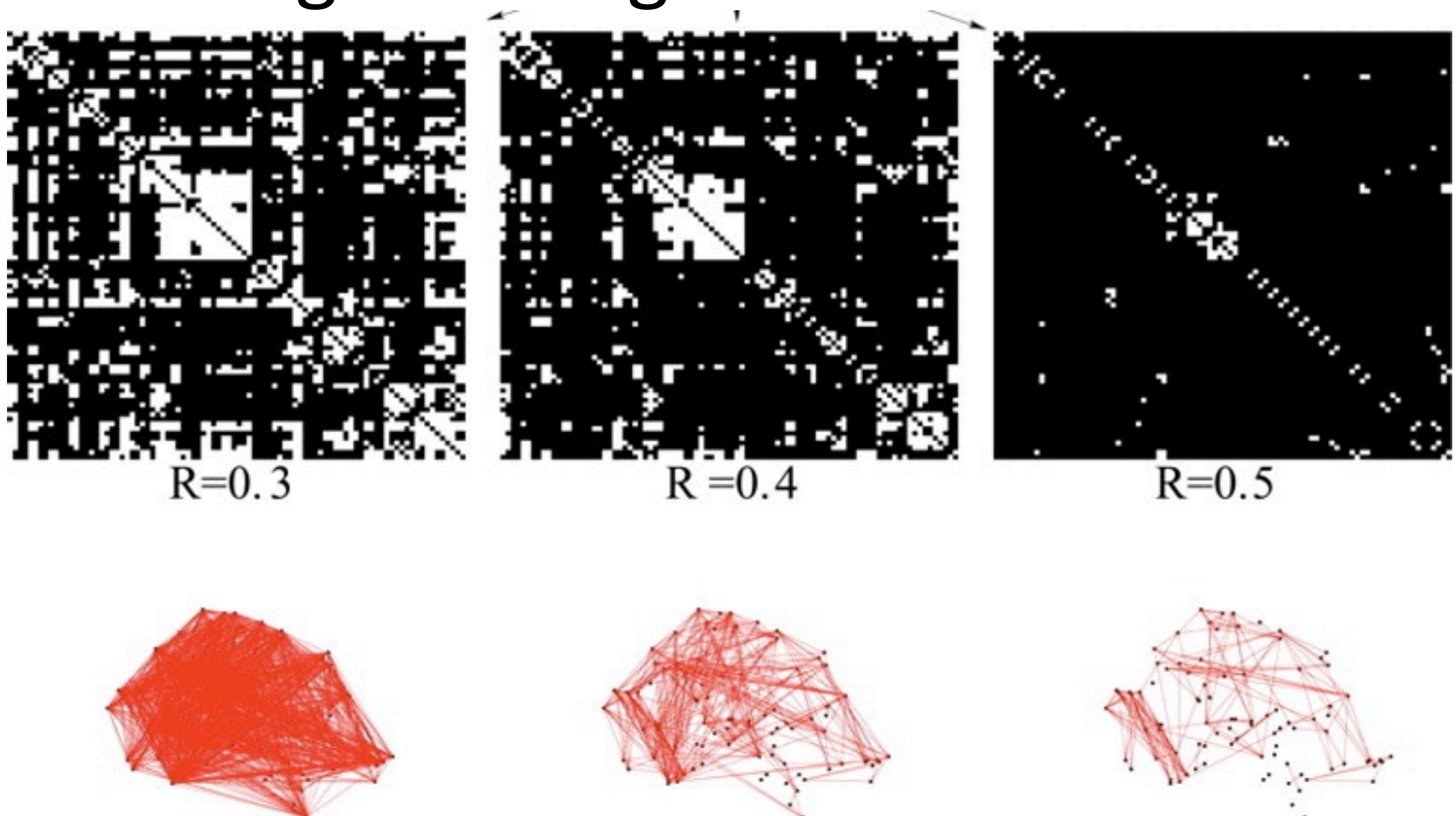


Fair… Petersen, PLoS Comp Bio 2009

Advantages of graph theory approaches

- Can make beautiful pictures (or ugly)
- Used for hypothesis generation and testing
  - Similarities between DTI & resting connectivity graphs (Honey, PNAS 2009)
- Can see how connections and segmentations change across populations
  - Graphs change in children with ADHD (Wang HBM 2008)
  - Graphs change with schizophrenia (Liu Brain 2008)
- The strength of seed-based correlations, with less worries about seed selection
- Potentially useful whole-brain-network metrics

Disadvantages of large-scale interconnections



Basset & Bullmore The Neuroscientist 2006

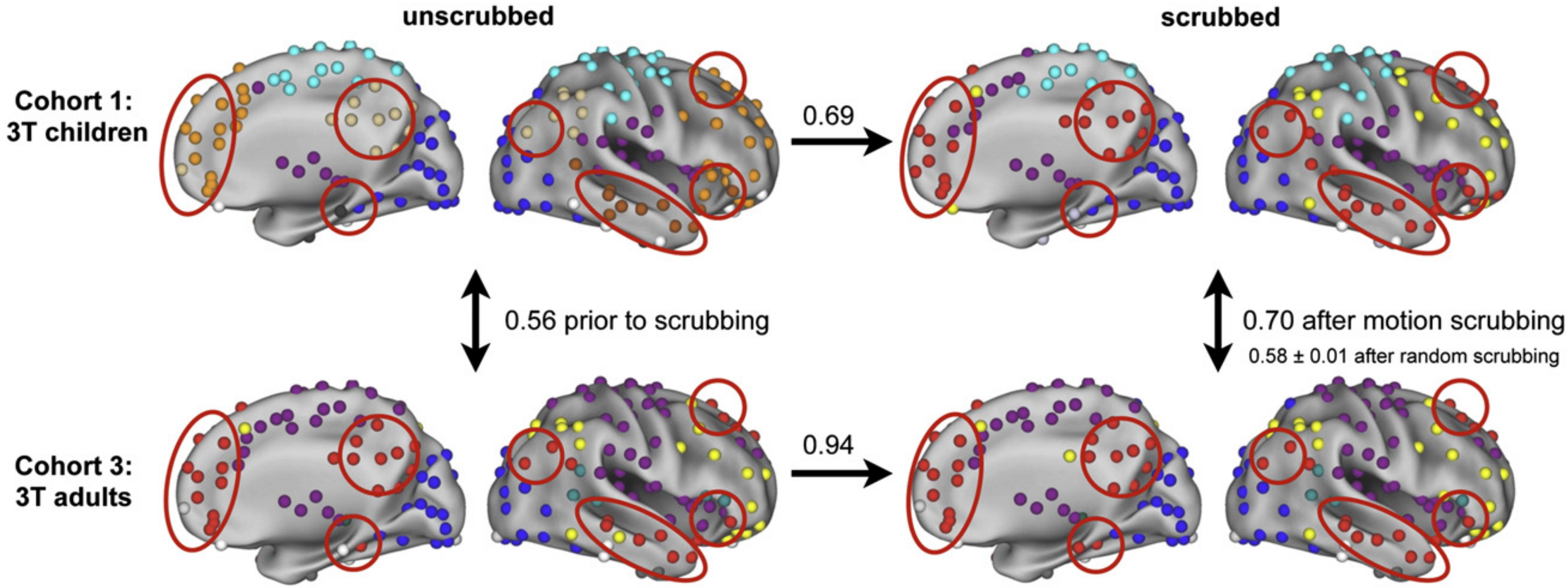
Sensitive to how you build the network

What is the region size

What is the distance function?

What is significant?

Preprocessing really matters



When they scrubbed data for areas of higher head motion (more common in children), the main network differences disappeared

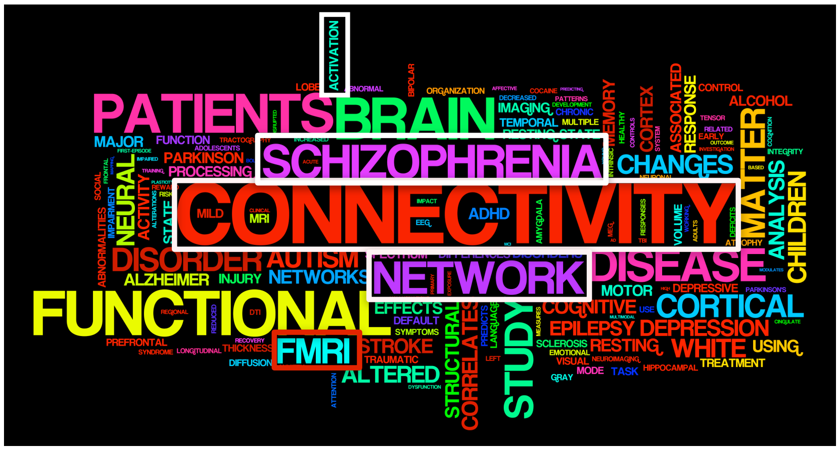
Power, … Petersen, Neuroimage 2012

“It really, really, really sucks. My favorite result of the last five years is an artifact,” Steve Petersen

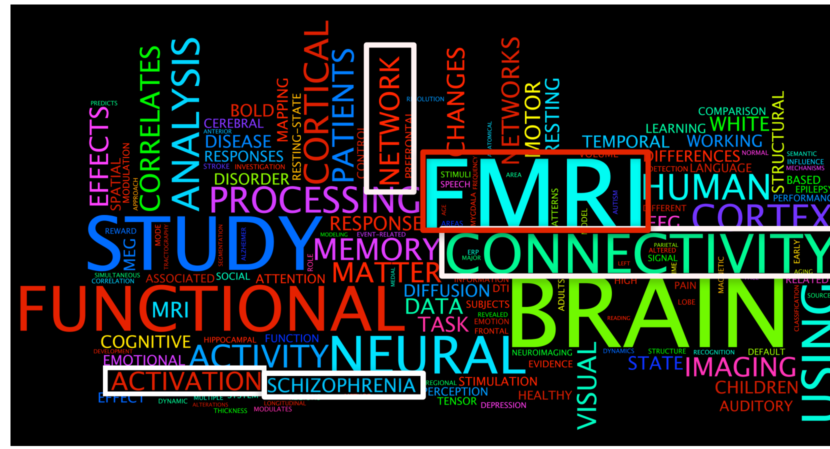
http://sfari.org/news-and-opinion/news/2012/movement-during-brain-scans-may-lead-to-spurious-patterns

For better and worse, connectivity now dominates fMRI methods development

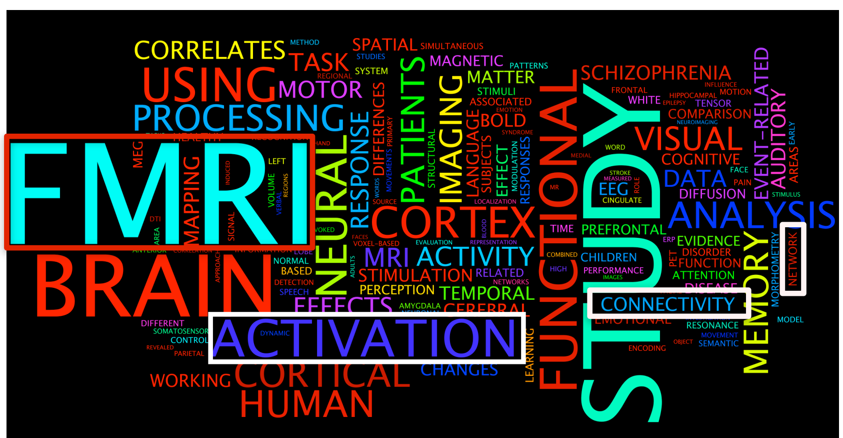
OHBM 2013



OHBM 2010-2012



OHBM 2003-2006



OHBM 2007-2009

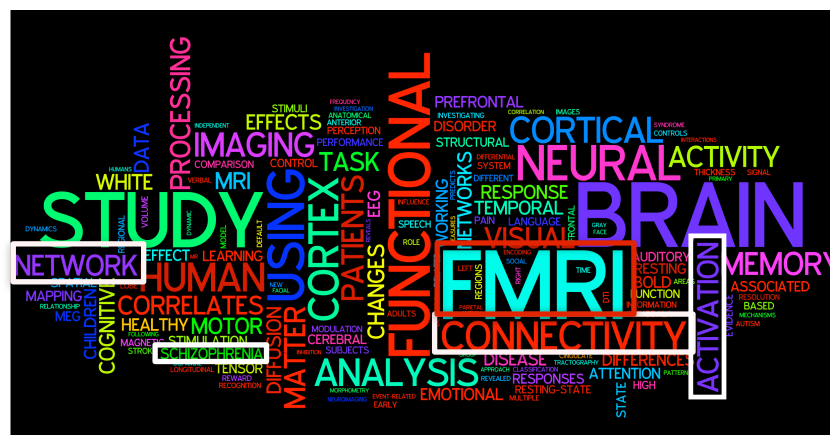


Image from Maurizio Corbetta

Resting-State Summary

- It’s really amazing this works!
- It’s not always easy to tell when it doesn’t work

Don’t forget the scientific questions

- How do we link functional connection maps to function?
- What differences are scientifically relevant?
- What disrupts fluctuations?
- How do we interpret differences across populations?

Come back next week

Catie Chang & Steve Gotts

- Methods to remove noise
  - How imperfect noise removal causes problems
- EEG-fMRI, MEG, ECoG
- Coritical layers with resting connectivity
- How connectivity changes over time
- More analysis methods
- Clinical applications
- The meaning of life

Acknowledgements

Slides and/or some talk ideas from

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